	L #	Hits	Search Text	DBs
1	L1	539	PROTEASE	USOCR
2	L2	104	PEPTIDASE	USOCR
3	L3	39803	HUMAN	USOCR
4	L4	3849	LUNG	USOCR
5	L5	1027	COLON	USOCR
6	L6	1070	OVARY	USOCR
7	L7	724	UTERUS	USOCR
8	L8	89	ENDOMETRIUM	USOCR
9	L9	29	BURKITT	USOCR
10	L10	54	(L1 OR L2) SAME L3	USOCR
11	L11	11	(L1 OR L2) SAME L4	USOCR
12	L12	0	(L1 OR L2) SAME L5	USOCR
13	L13	1	(L1 OR L2) SAME L6	USOCR
14	L14	1	(L1 OR L2) SAME L7	USOCR
15	L15	0	(L1 OR L2) SAME L8	USOCR
16	L16	0	(L1 OR L2) SAME L9	USOCR
17	L17	13	L11 OR L13 OR L14	USOCR

	L #	Hits	Search Text	DBs
1	L1	32924	PROTEASE OR PEPTIDASE	USPAT
2	L2	308965	HUMAN	USPAT
3	L3	7485	L1 SAME L2	USPAT
4	L4	3217	L1 NEAR10 L2	USPAT
5	L5	2512	L1 NEAR5 L2	USPAT
6	L6	672	L1 NEAR L2	USPAT
7	L7	152	L2 ADJ L1	USPAT
8	L8	1728	BURKITT	USPAT
9	L10	0	PRESENSILIN	USPAT
10	L11	147	PRESENILIN	USPAT
11	L12	55	L11 AND L3	USPAT
12	L9	61	L5 AND L8	USPAT
13	L13	1743	ENDOMETRIUM	USPAT
14	L15	39	L13 AND L5	USPAT
15	L14	126	L13 AND L3	USPAT
16	L16	46818	LUNG	USPAT
17	L17	2735	L16 AND L3	USPAT
18	L18	910	L16 AND L5	USPAT
19	L19	261	L16 AND L6	USPAT
20	L20	27472	SERINE	USPAT
21	L21	4664	L20 ADJ3 L1	USPAT
22	L22	4575	L20 ADJ L1	USPAT
23	L23	3927	L22 AND L2	USPAT
24	L24	694	L22 NEAR5 L2	USPAT
25	L25	533	L22 NEAR3 L2	USPAT
26	L26	251	L22 NEAR L2	USPAT

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FILE 'CAPLUS' ENTERED AT 09:53:59 ON 03 NOV 2003

=> S PROTEASE;S PEPTIDASE;S HUMAN
         77890 PROTEASE
         29608 PROTEASES
L1       91402 PROTEASE
                (PROTEASE OR PROTEASES)


         11053 PEPTIDASE
          4450 PEPTIDASES
L2       13140 PEPTIDASE
                (PEPTIDASE OR PEPTIDASES)


       1191734 HUMAN
        310510 HUMANS
L3     1351407 HUMAN
                (HUMAN OR HUMANS)

=> S (L1 OR L2) AND L3
L4       26055 (L1 OR L2) AND L3

=> S (L1 OR L2) (4A) L3
L5        5300 (L1 OR L2) (4A) L3

=> S BURKITT
          2940 BURKITT
           119 BURKITTS
L6        2957 BURKITT
                (BURKITT OR BURKITTS)

=> S L5 AND L6
L7           3 L5 AND L6

=> D 1-3

L7   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2003 ACS on STN
AN   2001:575654  CAPLUS
DN   136:214423
TI   .alpha.v.beta.3 integrin engagement modulates cell adhesion,
     proliferation, and   ***protease***   secretion in   ***human***
     lymphoid tumor cells
AU   Vacca, A.; Ria, R.; Presta, M.; Ribatti, D.; Iurlaro, M.; Merchionne, F.;
     Tanghetti, E.; Dammacco, F.
CS   Departments of Biomedical Sciences and Human Oncology, University of Bari
     Medical School, Bari, Italy
SO   Experimental Hematology (New York, NY, United States) (2001), 29(8),
     993-1003
     CODEN: EXHMA6; ISSN: 0301-472X
PB   Elsevier Science Inc.
DT   Journal
LA   English
RE.CNT  37    THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2003 ACS on STN
AN   2000:628010  CAPLUS
DN   133:217681
TI   Inhibitors of serine protease activity, and methods and compositions for
     treatment of herpes virus infections
IN   Shapiro, Leland
PA   The Trustees of University Technology Corporation, USA
SO   PCT Int. Appl., 89 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 4
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
PI   WO 2000051625       A1   20000908      WO 2000-US5557   20000303
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W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI US 1999-123167P P 19990305
US 1999-153942P P 19990915
OS MARPAT 133:217681
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1994:126417 CAPLUS
DN 120:126417
TI Met-ase: Cloning and distinct chromosomal location of a serine ***protease*** preferentially expressed in ***human*** natural killer cells
AU Smyth, Mark J.; Sayers, Thomas J.; Wiltrout, Theresa; Powers, James C.; Trapani, Joseph A.
CS Austin Res. Inst., Austin Hosp., Heidelberg, 3084, Australia
SO Journal of Immunology (1993), 151(11), 6195-205
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English

=> S RHOMBOID
461 RHOMBOID
153 RHOMBOIDS
L8 595 RHOMBOID
(RHOMBOID OR RHOMBOIDS)

=> S L5 AND L8
L9 1 L5 AND L8

=> D CBIB ABS

L9 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
2002:889039 Document No. 138:1666 Detection, cloning, characterization, sequences, and drug screening and therapeutic use of ***Rhomboid*** proteases. Freeman, Matthew (Medical Research Council, UK). PCT Int. Appl. WO 2002093177 A2 20021121, 110 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB2234 20020513. PRIORITY: GB 2001-11574 20010511; GB 2001-23261 20010927.
AB The present invention relates to proteins of the conserved ***Rhomboid*** family, which are involved in various signaling pathways within cells. ***Rhomboid*** proteins are found to possess a novel serine protease activity which cleaves within the transmembrane domain of a polypeptide substrate including EGFR ligands, such as Spitz protein. The present anal. of the mechanism and structure of ***Rhomboid*** has led to the discovery of a previously unknown gene (RHBDL3, ***Rhomboid*** -3) in the human genome which encodes a ***Rhomboid*** polypeptide. This gene occupies 68 kb on chromosome 17 between the annotated genes NJMU-R1 and FLJ11040 (contig NT 010799). The cDNA sequence and the encoded amino acid sequence of the human RHBDL3 are disclosed. The present inventors have also identified and cloned a zebrafish RHBDL2 (***Rhomboid*** -2) gene. The nucleotide sequence and the encoded amino acid sequence of the zebrafish RHBDL2 are provided. A compn. including a polypeptide or polypeptide fragment according to the invention may be used in prophylactic and/or therapeutic treatment.

Various aspects of the present invention relate to screening and assay methods and means, and substances identified thereby, for example, assays for substances which inhibit interaction between a ***Rhomboid*** polypeptide of the invention and a polypeptide substrate or between a Star polypeptide and a polypeptide substrate. Activity of a ***Rhomboid*** polypeptide may be detd. by detg. the prodn. of proteolytically cleaved substrate. Assays for detg. the ***Rhomboid*** activity are provided.

=> S PRESENILIN
1511 PRESENILIN
1373 PRESENILINS
L10 1715 PRESENILIN
(PRESENILIN OR PRESENILINS)

=> S L5 AND L10
L11 10 L5 AND L10

=> D 1-10 CBIB ABS

L11 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
2003:377127 Document No. 138:381349 ***Human*** signal peptide ***peptidase*** activity toward hepatitis C virus core-E1 region and its use for identifying candidate agents for affecting a viral infection. McLauchlan, John; Martoglio, Bruno (Medical Research Council, UK). PCT Int. Appl. WO 2003040684 A2 20030515, 144 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB5016 20021107. PRIORITY: GB 2001-26782 20011107.

AB A method for identifying a candidate agent for affecting a viral infection is described. The method comprises: (a) providing a first component comprising a signal peptide peptidase (SPPase) targeting sequence; (b) providing a second component comprising a SPPase as a second component; (c) contacting the two components with an agent to be tested under conditions that would permit the two components to interact in the absence of the agent; and (d) detg. whether the agent disrupts the interaction between the first and second components. Preferably, the SPPase targeting sequence is derivable from hepatitis C virus (HCV) core protein or a deriv., variant, or homolog thereof. The invention is based on the discovery that a human SPPase cleavage of the HCV polyprotein is crit. to allow release of the HCV-core from the endoplasmic reticulum (ER) membrane which then localizes in the cytoplasm. Cleavage by SPPase follows signal peptidase cleavage of the HCV polyprotein in a sequential manner and occurs at the junction of core-E1 sequences. Release from the ER membrane and degrdn. of an unstable form of HCV core is inhibited by abolishing SPPase cleavage. Thus, SPPase is proposed to be a ***presenilin*** -related, ER-localized aspartyl protease that promotes intramembrane proteolysis of signal peptides. Catalysis of HCV-core by SPPase which then promotes core to assoc. with intracellular lipid globules in the cytosol represents a target for therapies designed to prevent or reduce the effects and/pr progression of HCV infection. In addn., a specific inhibitor deriv. of (Z-Leu-Leu)2 ketone is identified which blocks SPPase processing of core in vitro with an IC50 of .apprx.50 nM.

L11 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
2003:358530 Document No. 139:241812 Random mutagenesis of PDZOmi domain and selection of mutants that specifically bind the Myc proto-oncogene and induce apoptosis. Junqueira, Daniela; Cilenti, Lucia; Musumeci, Lucia; Sedivy, John M.; Zervos, Antonis S. (Biomolecular Science Center and Department of Molecular Biology and Microbiology, University of Central Florida (UCF), Orlando, FL, 32826, USA). Oncogene, 22(18), 2772-2781 (English) 2003. CODEN: ONCNES. ISSN: 0950-9232. Publisher: Nature Publishing Group.

AB Omi is a mammalian serine protease that is localized in the mitochondria and released to the cytoplasm in response to apoptotic stimuli. Omi

induces cell death in a caspase-dependent manner by interacting with the X-chromosome linked inhibitor of apoptosis protein, as well as in a caspase-independent way that relies on its proteolytic activity. Omi is synthesized as a precursor polypeptide and is processed to an active serine protease with a unique PDZ domain. PDZ domains recognize the extreme carboxyl terminus of target proteins. Internal peptides that are able to fold into a .beta.-finger are also reported to bind some PDZ domains. Using a modified yeast two-hybrid system, PDZOmi mutants were isolated by their ability to bind the carboxyl terminus of human Myc oncoprotein in yeast as well as in mammalian cells. One such PDZm domain (PDZ-M1), when transfected into mammalian cells, was able to bind to endogenous Myc protein and induce cell death. PDZ-M1-induced apoptosis was entirely dependent on the presence of Myc protein and was not obsd. when c-myc null fibroblasts were used. Our studies indicate that the PDZ domain of Omi can provide a prototype that could easily be exploited to target specifically and inactivate oncogenes by binding to their unique carboxyl terminus.

L11 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
2003:346420 Document No. 139:159884 Targeting ***Presenilin*** -type Aspartic Protease Signal Peptide Peptidase with .gamma.-Secretase Inhibitors. Weihofen, Andreas; Lemberg, Marius K.; Friedmann, Elena; Rueeger, Heinrich; Schmitz, Albert; Paganetti, Paolo; Rovelli, Giorgio; Martoglio, Bruno (Institute of Biochemistry, Swiss Federal Institute of Technology (ETH), ETH-Hoenggerberg, Zurich, 8093, Switz.). Journal of Biological Chemistry, 278(19), 16528-16533 (English) 2003. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.
AB ***Presenilin*** is implicated in the pathogenesis of Alzheimer's disease. It is thought to constitute the catalytic subunit of the .gamma.-secretase complex that catalyzes intramembrane cleavage of .beta.-amyloid precursor protein, the last step in the generation of amyloidogenic A.beta. peptides. The latter are major constituents of amyloid plaques in the brain of Alzheimer's disease patients. Inhibitors of .gamma.-secretase are considered potential therapeutics for the treatment of this disease because they prevent prodn. of A.beta. peptides. Recently, the authors discovered a family of ***presenilin*** -type aspartic proteases. The founding member, signal peptide peptidase, catalyzes intramembrane cleavage of distinct signal peptides in the endoplasmic reticulum membrane of animals. In ***humans*** , the ***protease*** plays a crucial role in the immune system. Moreover, it is exploited by the hepatitis C virus for the processing of the structural components of the virion and hence is an attractive target for anti-infective intervention. Signal peptide peptidase and ***presenilin*** share identical active site motifs and both catalyze intramembrane proteolysis. These common features let the authors speculate that .gamma.-secretase inhibitors directed against ***presenilin*** may also inhibit signal peptide peptidase. Here the authors demonstrate that some of the most potent known .gamma.-secretase inhibitors efficiently inhibit signal peptide peptidase. However, the authors found compds. that showed higher specificity for one or the other protease. The authors findings highlight the possibility of developing selective inhibitors aimed at reducing A.beta. generation without affecting other intramembrane-cleaving aspartic proteases.

L11 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
2003:173459 Document No. 138:217451 Preparation, substrate specificity, and therapeutic uses of ***human*** .gamma.3 ***protease*** involved in processing of amyloid precursor protein. Crouthamel, Ming-Chih; Gardell, Stephen J.; Huang, Qian; Lai, Ming-Tain; Li, Yueming (Merck & Co., Inc., USA). PCT Int. Appl. WO 2003018050 A1 20030306, 48 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US26969 20020808. PRIORITY: US 2001-PV311410 20010810.
AB The invention provides .gamma.3 protease, a novel aspartyl class protease that is capable of taking part in the processing of amyloid precursor protein (APP) to A.beta. peptide. The .gamma.3 protease may be involved in the development and/or progression of Alzheimer's disease. It has a Mr of 60-120 kDa on gel filtration, and its activity is inhibited by pepstatin A but not by L685,458 (a known .gamma.-secretase inhibitor) with

a pH optimum of 6.0. .gamma.3 Protease cleaves amyloid precursor protein, as well as artificial substrates incorporating portions of APP695, at the same or similar sites as .gamma.-secretase, but can be distinguished from the known .gamma.-secretase activity involving ***presenilin*** -1 and ***presenilin*** -2. Methods of assaying .gamma.3 protease and identifying potential inhibitors, useful in the prevention or treatment of Alzheimer s disease, are disclosed.

L11 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
2002:495246 Document No. 137:259144 Identification of signal peptide peptidase, a ***presenilin*** -type aspartic protease. Weihofen, Andreas; Binns, Kathleen; Lemberg, Marius K.; Ashman, Keith; Martoglio, Bruno (Inst. Biochemistry, Swiss Federal Inst. Technology, Zurich, 8093, Switz.). Science (Washington, DC, United States), 296(5576), 2215-2218 (English) 2002. CODEN: SCIEAS. ISSN: 0036-8075. Publisher: American Association for the Advancement of Science.
AB Signal peptide peptidase (SPP) catalyzes intramembrane proteolysis of some signal peptides after they have been cleaved from a preprotein. In humans, SPP activity is required to generate signal sequence-derived human lymphocyte antigen-E epitopes that are recognized by the immune system, and to process hepatitis C virus core protein. We have identified human SPP as a polytopic membrane protein with sequence motifs characteristic of the ***presenilin*** -type aspartic proteases. SPP and potential eukaryotic homologs may represent another family of aspartic proteases that promote intramembrane proteolysis to release biol. important peptides.

L11 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
2002:71784 Document No. 136:97313 Transgenic mouse expressing human antichymotrypsin gene as Alzheimer's disease model and uses in drug screening. Nilsson, Lars; Potter, Huntington; Arendash, Gary W. (University of South Florida, USA). PCT Int. Appl. WO 2002005634 A2 20020124, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US22186 20010713. PRIORITY: US 2000-PV218054 20000713.
AB The invention provides a transgenic mouse that expresses human antichymotrypsin (ACT) in brain tissues as an Alzheimer's disease model together with animal tissue-derived cell lines and progeny animals of the transgenic mouse. In particular, the transgenic mouse carries an human ACT gene under the control of 5' untranslated region and promoter of a glial fibrillary acidic protein (GFAP) gene, and exhibits symptoms similar to Alzheimer's disease. The invention also provides primary cell cultures, and cell lines derived from the parent transgenic animal carrying ACT gene. Progeny are obtained by mating the transgenic animal with select animal strains used as models of Alzheimer's disease, related neurol. disorders, or amyloidogenic diseases. The invention further provides methods utilizing the parent and progeny mice and cells derived from the transgenic mouse to screen drugs for use as anti-inflammatory drugs, inhibitors of amyloidogenesis, and/or inhibitors of tau protein pathol. assocd. with Alzheimer's disease, in the treatment of a variety of neurol. diseases.

L11 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
2000:154800 Document No. 132:304987 ***Human*** aspartic ***protease*** memapsin 2 cleaves the .beta.-secretase site of .beta.-amyloid precursor protein. Lin, Xinli; Koelsch, Gerald; Wu, Shili; Downs, Debbie; Dashti, Azar; Tang, Jordan (Protein Studies Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104, USA). Proceedings of the National Academy of Sciences of the United States of America, 97(4), 1456-1460 (English) 2000. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.
AB The cDNAs of two new ***human*** membrane-assocd. aspartic ***proteases*** , memapsin 1 and memapsin 2, have been cloned and sequenced. The deduced amino acid sequences show that each contains the typical pre, pro, and aspartic protease regions, but each also has a C-terminal extension of over 80 residues, which includes a single

transmembrane domain and a C-terminal cytosolic domain. Memapsin 2 mRNA is abundant in human brain. The protease domain of memapsin 2 cDNA was expressed in Escherichia coli and was purified. Recombinant memapsin 2 specifically hydrolyzed peptides derived from the .beta.-secretase site of both the wild-type and Swedish mutant .beta.-amyloid precursor protein (APP) with over 60-fold increase of catalytic efficiency for the latter. Expression of APP and memapsin 2 in HeLa cells showed that memapsin 2 cleaved the .beta.-secretase site of APP intracellularly. These and other results suggest that memapsin 2 fits all of the criteria of .beta.-secretase, which catalyzes the rate-limiting step of the in vivo prodn. of the .beta.-amyloid (A.beta.) peptide leading to the progression of Alzheimer's disease. Recombinant memapsin 2 also cleaved a peptide derived from the processing site of ***presenilin*** 1, albeit with poor kinetic efficiency. Alignment of cleavage site sequences of peptides indicates that the specificity of memapsin 2 resides mainly at the S1' subsite, which prefers small side chains such as Ala, Ser, and Asp.

L11 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
1998:180682 Document No. 128:241248 A ***human*** serine ***protease*** that cleaves ***presenilins*** and cloning and expression of a cDNA encoding it and their therapeutic uses. Karran, Eric H.; Clinkenbeard, Helen E.; Browne, Michael J.; Southan, Christopher D.; Creasy, Caretha L.; Livi, George P. (Smithkline Beecham Plc, UK; Smithkline Beecham Corp.). Eur. Pat. Appl. EP 828003 A2 19980311, 65 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI. (English). CODEN: EPXXDW. APPLICATION: EP 1997-306501 19970826. PRIORITY: US 1996-25436 19960906; US 1996-27873 19961025; US 1996-32875 19961213.

AB Serine proteinases that cleave ***presenilins*** and that may play a role in the etiol. of Alzheimer's disease are identified and cDNAs encoding them are cloned and expressed. The enzymes may be useful in the therapeutic correction of aberrant ***presenilin*** processing in the treatment of Alzheimer's disease. CDNAs for proteins interacting with ***presenilins*** were identified using a two-hybrid system. CDNAs for four isoenzymes were obtained. The mRNA for one of these isoenzymes was found in all tissues tested.

L11 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
1998:81580 Document No. 128:191179 Alzheimer's Disease Associated ***Presenilin*** -1 Holoprotein and Its 18-20 kDa C-Terminal Fragment Are Death Substrates for Proteases of the Caspase Family. Gruenberg, Juergen; Walter, Jochen; Loetscher, Hansruedi; Deuschle, Ulrich; Jacobsen, Helmut; Haass, Christian (Department of Molecular Biology, Central Institute of Mental Health, Mannheim, 68159, Germany). Biochemistry, 37(8), 2263-2270 (English) 1998. CODEN: BICHAW. ISSN: 0006-2960. Publisher: American Chemical Society.

AB Mutations in the ***presenilin*** (PS) genes are linked to early-onset familial Alzheimer's disease (FAD). PS-1 proteins are proteolytically processed by an unknown protease leading to the formation of two stable fragments of .apprx.30 and .apprx.20 kDa. In addn. to the conventional fragments, alternative cleavage products were obsd. as well. Here, the authors characterize an alternative proteolytic pathway of PS-1 which involves proteases of the caspase superfamily. Caspase-mediated cleavage occurs between aspartate 345 and serine 346 C-terminal to the conventional cleavage detd. previously. Full-length PS-1 can serve as a substrate for caspase-like proteases, as demonstrated by the generation of the alternative C-terminal fragment in cells expressing PS-1 contg. the .DELTA.exon 10 deletion which is known to accumulate as a full-length mol. By inhibition of de novo protein synthesis in untransfected cells, the authors demonstrate that the conventional C-terminal fragment of PS-1 is a substrate for caspase-like proteases as well. Therefore, full-length and the conventional C-terminal fragment of PS-1 can serve as potential death substrates. Due to the fact that very little full-length PS-1 is expressed in vivo, the much more abundant C-terminal fragment and not the full-length precursor is the major in vivo substrate for the alternative cleavage of PS-1 by proteases of the caspase superfamily.

L11 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
1997:707930 Document No. 128:32796 ***Presenilin*** -1, amyloid precursor protein and amyloid precursor-like protein 2 mRNA levels in human superior frontal cortex during aging. Flood, Fiona M.; Cowburn, Richard F.;

Johnston, Janet A. (Department of Clinical Neuroscience and Family Medicine, Geriatric Section, Karolinska Institute, Novum KFC, 141 86, Huddinge, Swed.). Neuroscience Letters, 235(1,2), 17-20 (English) 1997. CODEN: NELED5. ISSN: 0304-3940. Publisher: Elsevier.

AB The ***presenilin*** -1 (PS-1) and amyloid precursor protein (APP) genes carry mutations which co-segregate with early-onset familial Alzheimer's disease. The APP and PS-1 gene products may be involved in the etiol. of the more common late onset form of Alzheimer's disease, where increasing age is a major risk factor. To investigate whether age affected mRNA expression of these genes, we quantified PS-1, total APP, APP contg. the kunitz-type protease inhibitor (KPI) domain and amyloid precursor-like protein 2 (APLP2) mRNAs in post-mortem superior frontal cortices from 23 control subjects aged 38 to 89 yr using soln. hybridization-RNase protection assays. PS-1, total APP, APP KPI and APLP2 mRNA levels were unchanged over this age range. PS-1 was the least abundant mRNA, at approx. 7% of total APP, the most highly expressed mRNA studied (10.8 copies/pg total RNA). The proportion of total APP encoding the KPI domain (.apprxeq.52%) was unaffected by age. APLP2 mRNA was present at .apprxeq.29% of the total APP mRNA level. Significant pos. correlations were present between total APP, APP KPI and APLP2 mRNA levels. These results indicate that the increased prevalence of Alzheimer's disease cannot be attributed to alterations in cortical PS-1, APP and APLP2 mRNA levels or APP KPI splicing during aging.

```
=> S DENDRITIC
         34450 DENDRITIC
             5 DENDRITICS
L12      34451 DENDRITIC
                (DENDRITIC OR DENDRITICS)

=> S L5 AND L12
L13         21 L5 AND L12

=> S L13 NOT (L7,L9,L11)
L14         21 L13 NOT ((L7 OR L9 OR L11))

=> D 1-21 CBIB ABS
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L14 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2003:778793 Differential expression and regulation of ***protease*** -activated receptors in ***human*** peripheral monocytes and monocyte-derived antigen-presenting cells. Colognato, Renato; Slupsky, Joseph R.; Jendrach, Marina; Burysek, Ladislav; Syrovets, Tatiana; Simmet, Thomas (Department of Pharmacology of Natural Products and Clinical Pharmacology, University of Ulm, Germany). Blood, 102(7), 2645-2652 (English) 2003. CODEN: BLOOAW. ISSN: 0006-4971. Publisher: American Society of Hematology.

AB Protease-activated receptors (PARs) are stimulated by proteolytic cleavage of their extracellular domain, unmasking a new N-terminus acting as tethered ligand. Whereas the role of PARs in platelets is well known, their presence and function in human monocytes and other antigen-presenting cells has not been characterized. Here it is demonstrated that human peripheral monocytes and monocyte-derived macrophages and ***dendritic*** cells differentially express PARs. Human monocytes express mainly PAR1 and less PAR3. Differentiation of monocytes into macrophages by either macrophage colony-stimulating factor (M-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) elicits enhanced expression of PAR1, PAR2, and PAR3. In contrast, ***dendritic*** cells differentiated from monocytes by GM-CSF and interleukin-4 (IL-4) strongly down-regulated PAR1, PAR2, and PAR3, both at the mRNA and the protein level. Down-regulation of the PAR expression was apparently due to IL-4, because treatment of macrophages with IL-4 caused down-regulation of PAR1, PAR2, and PAR3. PAR4 mRNA expression remained undetectable in any of the cell types investigated. Stimulation of PAR1, PAR2, and PAR3 with thrombin, trypsin, or established receptor-activating peptides (PAR-APs) triggered cytosolic Ca2+ responses, indicating functionally active PARs. Further, stimulation of monocytes or macrophages with thrombin or PAR1-AP, but not with PAR2-or PAR4-AP, triggers expression of monocyte chemoattractant protein-1 (MCP-1) both at the mRNA and the protein level. These data demonstrate that

differentiation of human monocytes is assocd. with differential expression of functionally active PARs that mediate distinct regulatory functions in inflammation and atherogenesis.

L14 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
2003:757195 Document No. 139:259468 Human matrix metalloproteinase 7 as a tumor marker, and diagnostic and therapeutic uses thereof. O'Brien, Timothy J. (USA). U.S. Pat. Appl. Publ. US 2003180736 A1 20030925, 75 pp., Cont.-in-part of U.S. Ser. No. 835,948, abandoned. (English). CODEN: USXXCO. APPLICATION: US 2002-172597 20020614. PRIORITY: US 1997-PV41404 19970319; US 1998-39211 19980314; US 2000-492543 20000127; US 2001-835948 20010416.
AB The invention claims nucleic acid primer sets, used in combination with quant. amplification (PCR) of tissue cDNA, that can indicate the presence of specific proteases in a tissue sample. Specifically, the present invention relates to expression of ***human*** PUMP-1 ***protease*** (matrix metalloprotease 7). The PUMP-1/MMP-7 protease is specifically over-expressed in certain cancers, and the mRNA presence may serve for early detection of assocd. ovarian and other malignancies. The invention also claims human MMP-7 cDNA sequences, antisense nucleic acids, MMP-7 peptides, and antibodies for the design of interactive therapies for cancer treatment. The invention includes methods of inhibiting MMP-7 mRNA expression or protease expression, producing immune-activated cells directed toward MMP-7 peptides, and methods for screening compds. that inhibit MMP-7 activity. Computer programs were used to rank PUMP-1 peptides for their potential as immunogens according to their predicted ability to bind HLA class I alleles. CD8+ cytotoxic T lymphocytes specific for PUMP-1 peptide 208-216 killed peptide-loaded autologous LCL and heterologous HLA A*0201-expressing peptide-loaded LCL but did not kill the controls.

L14 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
2003:661477 Document No. 139:229120 Cathepsin V is involved in the degradation of invariant chain in human thymus and is overexpressed in myasthenia gravis. Tolosa, Eva; Li, Weijie; Yasuda, Yoshiyuki; Wienhold, Wolfgang; Denzin, Lisa K.; Lautwein, Alfred; Driessen, Christoph; Schnorrer, Petra; Weber, Ekkehard; Stevanovic, Stefan; Kurek, Raffael; Melms, Arthur; Broemme, Dieter (Department of Neurology, Tuebingen University Hospital, Tuebingen University, Tuebingen, Germany). Journal of Clinical Investigation, 112(4), 517-526 (English) 2003. CODEN: JCINAO. ISSN: 0021-9738. Publisher: American Society for Clinical Investigation.
AB Stepwise degrdn. of the invariant chain (Ii) is required for the binding of antigenic peptides to MHC class II mols. Cathepsin (Cat) L in the murine thymus and Cat S in peripheral APCs have both been implicated in the last step of Ii degrdn. that gives rise to the class II-assocd. invariant chain peptides (CLIP). Cat V has been recently described as highly homologous to Cat L and exclusively expressed in human thymus and testis, but with no mouse orthologue. We report that Cat V is the dominant cysteine ***protease*** in cortical ***human*** thymic epithelial cells, while Cat L and Cat S seem to be restricted to ***dendritic*** and macrophage-like cells. Active Cat V in thymic lysosomal prepns. was demonstrated by active-site labeling. Recombinant Cat V was capable of converting Ii into CLIP efficiently, suggesting that Cat V is the protease that controls the generation of .alpha..beta.-CLIP complexes in the human thymus, in analogy to Cat L in mouse. Comparison of Cat V expression between thymi from patients with myasthenia gravis and healthy controls revealed a significantly higher expression level in the pathol. samples, suggesting a potential involvement of this protease in the immunopathogenesis of myasthenia gravis, an autoimmune disease almost invariably assocd. with thymic pathol.

L14 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
2003:423945 Document No. 139:163523 Immunostimulatory properties of proteases: serine danger. Schoenecker, Jonathan Gregory (Duke Univ., Durham, NC, USA). 104 pp. Avail. UMI, Order No. DA3063203 From: Diss. Abstr. Int., B 2003, 63(9), 4112 (English) 2002.
AB Unavailable

L14 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
2003:319344 Document No. 138:349663 Hepsin protease as a tumor marker, and methods for the early diagnosis and therapy of ovarian cancer and other

malignancies. O'Brien, Timothy J.; Cannon, Martin J.; Santin, Alessandro (USA). U.S. Pat. Appl. Publ. US 2003077618 A1 20030424, 43 pp., Cont.-in-part of U.S. Ser. No. 102,283. (English). CODEN: USXXCO. APPLICATION: US 2002-135795 20020430. PRIORITY: US 2000-510738 20000222; US 2001-861966 20010521; US 2001-919048 20010730; US 2002-102283 20020320.

AB The disclosed nucleic acid primer sets, used in combination with quant. amplification (PCR) of tissue cDNA, can indicate the presence of specific proteases in a tissue sample. Specifically, the present invention relates to expression of hepsin protease. The detected proteases are themselves specifically over-expressed in certain cancers, and the presence of their genetic precursors may serve for early detection of assocd. ovarian and other malignancies, and for the design of interactive therapies for cancer treatment. There are provided methods of vaccinating an individual against hepsin or produce immune-activated cells directed toward hepsin by inoculating an individual with an expression vector encoding a hepsin protein or a fragment thereof. In another embodiment of the present invention, there are provided compns. comprising immunogenic fragments of hepsin protein or an oligonucleotide having a sequence complementary to hepsin coding sequence. In another embodiment of the present invention, there is provided a method of screening for compds. that inhibit hepsin activity.

L14 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2003:238911 Document No. 138:400046 An essential role for tripeptidyl peptidase in the generation of an MHC class I epitope. Seifert, Ulrike; Maranon, Concepcion; Shmueli, Ayelet; Desoutter, Jean-Francois; Wesoloski, Lisa; Janek, Katharina; Henklein, Peter; Diescher, Susanne; Andrieu, Muriel; de la Salle, Henri; Weinschenk, Toni; Schild, Hansjoerg; Laderach, Diego; Galy, Anne; Haas, Gaby; Kloetzel, Peter-M.; Reiss, Yuval; Hosmalin, Anne (Institut fuer Biochemie-Charite, Medical Faculty of the Humboldt-University Berlin, Berlin, 10117, Germany). Nature Immunology, 4(4), 375-379 (English) 2003. CODEN: NIAMCZ. ISSN: 1529-2908. Publisher: Nature Publishing Group.

AB Most of the peptides presented by major histocompatibility complex (MHC) class I mols. require processing by proteasomes. Tripeptidyl peptidase II (TPPII), an aminopeptidase with endoproteolytic activity, may also have a role in antigen processing. Here, the authors analyzed the processing and presentation of the immunodominant human immunodeficiency virus epitope HIV-Nef(73-82) in human ***dendritic*** cells. The authors found that inhibition of proteasome activity did not impair Nef(73-82) epitope presentation. In contrast, specific inhibition of TPPII led to a redn. of Nef(73-82) epitope presentation. The authors propose that TPPII can act in combination with or independent of the proteasome system and can generate epitopes that evade generation by the proteasome-system.

L14 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2003:8201 Document No. 138:35285 Protein and cDNA sequences of a novel ***human*** cysteine ***protease*** HIPHUM134, and therapeutic uses thereof. Chen, Jingwen; Ink, Barbara Susan; Lewis, Alan Peter (Glaxo Group Limited, UK). Brit. UK Pat. Appl. GB 2372994 A1 20020911, 37 pp. (English). CODEN: BAXXDU. APPLICATION: GB 2001-28025 20011122. PRIORITY: GB 2000-28761 20001124.

AB The invention provides protein and cDNA sequences of a novel human cysteine proteinase, referred to herein as HIPHUM134. HIPHUM134 is shown to be expressed in all tissues at various levels. It is highly expressed in adrenal, cerebellum, jejunum, lung, rectum, testis, tonsil and urinary bladder. It is also expressed at significant levels in fetal brain, ovary, thymus, thyroid and uterus. In addn., HIPHUM134 is expressed in T cells, peripheral blood mononuclear cells (PBMCs), monocytes and ***dendritic*** cells. The novel cysteine proteinase is a screening target for the identification and development of novel pharmaceutical agents, including modulators of cysteine proteinase activity. These agents may be used in the treatment and/or prophylaxis of disorders such as Cushing's disease, Addison's disease, hypertension, hyperkalemia, hypokalemia, polycystic ovary, infertility, hirsutism and other metabolic diseases, HBV infection, HIV infection, HSV infection, breast cancer, Huntington's disease, central areolar choroidal dystrophy, lung edemas, obesity, alcoholism and juvenile cystic kidneys.

L14 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2003:6093 Document No. 138:68924 Protein and cDNA sequences of a

human ***dendritic*** cell transmembrane serine ***protease*** (DCTSP) and uses in drug screening. Anderson, Dirk M.; Virca, G. Duke (Immunex Corporation, USA). PCT Int. Appl. WO 2003000850 A2 20030103, 58 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US19708 20020620. PRIORITY: US 2001-PV299606 20010620.

AB The invention provides protein and cDNA sequences of ***human*** ***dendritic*** cell transmembrane serine ***protease*** and its splice variant. The isolated serine proteases can be used to hydrolyze peptide bonds. The serine proteases are also useful in screening for inhibitors or agonists thereof.

L14 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2002:754547 Document No. 137:277784 Subtilisin protease and variants with reduced allergenicity for use in pharmaceutical, cleaning and cosmetic products. Estell, David A.; Ganshaw, Grant C.; Harding, Fiona A.; Larenas, Edmund A.; Poulose, Ayrookaran J.; Sikorski, Elizabeth Ellen; Elliott, Russel Philip (Genencor International, Inc., USA; The Procter & Gamble Company). PCT Int. Appl. WO 2002077187 A2 20021003, 90 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US9205 20020322. PRIORITY: US 2001-PV278459 20010323.

AB The present invention relates to novel protein variants that exhibit reduced allergenicity when compared to the parental proteins. Also included are DNA mols. that encode the novel variants, host cells comprising the DNA and methods of making proteins less allergenic. The protein variants are e.g. Bacillus amyloliquefaciens subtilisin protease and its substitution, deletion or addn. mutants having altered T cell epitope. The subtilisin and variants are useful in compns. including pharmaceutical, laundry, cosmetic, dish, hard surface, skin care, hair care, beauty care, oral care and contact lens.

L14 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2002:746448 Document No. 138:34153 cDNAs encoding ***human*** cysteine ***protease*** HIPHUM 106 and drug screening for treatment of respiratory diseases, asthma, rheumatoid arthritis and cancer. Chen, Jingwen; Ink, Barbara Susan; Lewis, Alan Peter (Glaxo Group Limited, UK). Brit. UK Pat. Appl. GB 2371801 A1 20020807, 32 pp. (English). CODEN: BAXXDU. APPLICATION: GB 2001-24035 20011005. PRIORITY: GB 2000-24449 20001005.

AB The present invention relates to the nucleic acids encoding human cysteine proteinase HIPHUM 106 that cleaves SUMO (small ubiquitin-related modifier) to generate its mature form. The cysteine proteinase HIPHUM 106 mRNA is highly expressed in adrenal gland, cerebellum, lung, omentum, rectum and testis and expressed at significant levels in adenoids, tonsils and spleen. Cysteine proteinase HIPHUM 106 mRNA levels are also elevated in lung asthma, lung COPD, stimulated bone marrow, T cells, peripheral blood mononuclear cells, monocytes, ***dendritic*** cells, RA synovium and differentiated osteoblasts. Expression levels are down regulated in breast carcinoma and to some extent in colon and lung carcinoma and bFGF endothelial cells. Methods of drug screening to identify effectors of cysteine proteinase HIPHUM 106 for treatment of respiratory diseases, asthma, rheumatoid arthritis and cancer are provided.

L14 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2002:126981 Document No. 137:244 Complementary antiviral efficacy of hydroxyurea and ***protease*** inhibitors in ***human***

immunodeficiency virus-infected ***dendritic*** cells and lymphocytes. Piccinini, Giampiero; Foli, Andrea; Comolli, Giuditta; Lisziewicz, Julianna; Lori, Franco (Research Institute for Genetic and Human Therapy at IRCCS Policlinico S. Matteo, Pavia, Italy). Journal of Virology, 76(5), 2274-2278 (English) 2002. CODEN: JOVIAM. ISSN: 0022-538X. Publisher: American Society for Microbiology.

AB ***Dendritic*** cells are susceptible to human immunodeficiency virus (HIV) infection and may transmit the virus to T cells in vivo. Scarce information is available about drug efficacy in ***dendritic*** cells because preclin. testing of antiretroviral drugs has been limited predominantly to T cells and macrophages. We compared the antiviral activities of hydroxyurea and two protease inhibitors (indinavir and ritonavir) in monocyte-derived ***dendritic*** cells and in lymphocytes. At therapeutic concns. (50 to 100 .mu.M), hydroxyurea inhibited supernatant virus prodn. from monocyte-derived ***dendritic*** cells in vitro but the drug was ineffective in activated lymphocytes. Concns. of hydroxyurea insufficient to be effective in activated lymphocytes cultured alone strongly inhibited supernatant virus prodn. from cocultures of uninfected, activated lymphocytes with previously infected monocyte-derived ***dendritic*** cells in vitro. In contrast, protease inhibitors were up to 30-fold less efficient in ***dendritic*** cells than in activated lymphocytes. Our data support the rationale for testing of the combination of hydroxyurea and protease inhibitors, since these drugs may have complementary antiviral efficacies in different cell compartments. A new criterion for combining drugs for the treatment of HIV infection could be to include at least one drug that selectively targets HIV in viral reservoirs.

L14 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2002:4937 Document No. 136:193743 Differential effects of HIV-1 protease inhibitors on ***dendritic*** cell immunophenotype and function. Gruber, Andreas; Wheat, Jeffery C.; Kuhen, Kelli L.; Looney, David J.; Wong-Staal, Flossie (Department of Medicine, University of California, San Diego, La Jolla, CA, 92093, USA). Journal of Biological Chemistry, 276(51), 47840-47843 (English) 2001. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB Recent findings show that ***human*** immunodeficiency virus (HIV)-1 ***protease*** inhibitors designed to specifically inhibit the aspartic protease of HIV-1 nonetheless exert various effects on immune cell function in vitro and in vivo. ***Dendritic*** cells (DC), central players of the immune system, express several aspartic proteases that are important for DC function. In the present study, we demonstrate that all of the HIV-1 protease inhibitors tested affect DC maturation. In addn., saquinavir had a strong inhibitory effect on the T-cell stimulatory capacity of mature DC. In contrast, indinavir had only a slight effect on DC induced T-cell proliferation and allowed efficient transduction of DC with a replication-incompetent HIV-1 vector designed for DC-based immunotherapy. HIV-1 protease inhibitors that have little or no effect on DC function may be preferable for combination with immunotherapy for HIV/AIDS.

L14 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2001:935793 Document No. 136:65261 ***Human*** ESP-1(eosinophil serine ***protease*** 1)-like serine protease and cDNA and their use in drug screening and disease diagnosis and treatment. Xiao, Yonghong (Bayer Aktiengesellschaft, Germany). PCT Int. Appl. WO 2001098503 A2 20011227, 131 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP6936 20010620. PRIORITY: US 2000-PV212844 20000621; US 2000-PV244171 20001031; US 2001-PV279766 20010330.

AB ***Human*** ESP-1(eosinophil serine ***protease*** 1)-like serine protease and cDNA are disclosed. Its mRNA expression profile in various human tissues, and immune cells is provided. Significant high expression of the ESP-1-like proteinases is detected in eosinophils and monocytes and they selectively promotes a subset of leukocytes, activated and

functioning T cells, B cells and ***dendritic*** cells to migrate into inflamed tissues. Over expression of ESP-1-like proteinases induces phenotype changes of A549 lung epithelial cells thus is implicated to be involved in the pathol. of asthma. Recombinant cells expressing this cDNA can be used to prep. the enzyme. These recombinant cells, the enzyme, or nucleic acids encoding the enzyme are useful in screening for modulators of the enzymic activity or gene expression. Methods of screening for its modulators and using them for the treatment of various disease models and testing their effectiveness are described. Reagents which regulate ***human*** ESP-1(eosinophil serine ***protease*** 1)-like serine protease activity and reagents which bind to ***human*** ESP-1(eosinophil serine ***protease*** 1)-like serine protease gene products can be used to regulate extracellular matrix degrdn. Such regulation is particularly useful for treating chronic inflammatory diseases including, but not limited to, asthma, airway allergy, osteoporosis, and chronic obstructive pulmonary disease.

L14 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2001:801109 Document No. 136:67361 The spectrum of ***human*** kallikrein 6 (zyme/ ***protease*** M/neurosin) expression in ***human*** tissues as assessed by immunohistochemistry. Petraki, Constantina D.; Karavana, Vassiliki N.; Skoufogiannis, Pavlos T.; Little, Sheila P.; Howarth, David J. C.; Yousef, George M.; Diamandis, Eleftherios P. (Department of Pathology, Evangelismos Hospital, Athens, Greece). Journal of Histochemistry and Cytochemistry, 49(11), 1431-1441 (English) 2001. CODEN: JHCYAS. ISSN: 0022-1554. Publisher: Histochemical Society, Inc..

AB The KLK6 gene is a new member of the human kallikrein gene family and encodes for a secreted ***protease*** , ***human*** kallikrein 6 (hK6; also known as zyme/protease M/neurosin). No study has as yet reported detailed immunohistochem. localization of hK6 in human tissues. Our purpose was to examine the expression of hK6 in human tissues by immunohistochem. We have analyzed 199 paraffin blocks from archival, current, and autopsy material prepd. from almost every normal human tissue. We employed an hK6-specific polyclonal rabbit antibody and avidin-biotin to localize hK6 by IHC. The staining pattern, the distribution of the immunostaining, and its intensity were studied in detail. The IHC expression of zyme was generally cytoplasmic. Various normal human tissues expressed the protein abundantly. Glandular epithelia constituted the main immunoexpression sites, with representative organs being the breast, prostate, kidney, endometrium, colon, appendix, salivary glands, bile ducts, and gallbladder. The small intestine, stomach, endocervix, Fallopian tube, epididymis, bronchus, and upper respiratory tract showed a focal expression as well. Choroid plexus epithelium, peripheral nerves, and some neuroendocrine cells (including the islets of Langerhans, cells in the anterior pituitary gland, and adrenal medulla) expressed the protein strongly and diffusely. A characteristic immunostaining was obsd. in the Hassall's corpuscles of the thymus, the oxyphilic cells of the thyroid and parathyroid glands, the primordial follicles of the ovary, ***dendritic*** cells mainly in the spleen, and in various cells of the placenta.

L14 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2001:754805 Document No. 136:95868 Therapeutic effects of cysteine protease inhibition in allergic lung inflammation: inhibition of allergen-specific T lymphocyte migration. Layton, G. T.; Harris, S. J.; Bland, F. A.; Lee, S. R.; Fearn, S.; Kaleta, J.; Wood, M. L.; Bond, A.; Ward, G. (British Biotech Pharmaceuticals plc, Oxford, OX4 5LY, UK). Inflammation Research, 50(8), 400-408 (English) 2001. CODEN: INREFB. ISSN: 1023-3830. Publisher: Birkhaeuser Verlag.

AB Objective and design: We have evaluated the effects of the broad-spectrum cysteine protease inhibitor E64 on allergic lung inflammation in the mouse ovalbumin model of human asthma. We have also characterized membrane-assocd. cathepsin enzyme activity on a range of cell types. Materials: Balb/C mice, E64 and CA074, various cell lines. Treatment: E64 was administered by s.c. minipump into ovalbumin-sensitized mice prior to intranasal ovalbumin challenge. The effect of E64 on ovalbumin-induced inflammation in vivo and ovalbumin-specific T cell proliferation in vitro and ex vivo was examd. Membrane-assocd. cathepsin activity on various cell types was measured. Results: E64 treatment (0.36-0.48 mg/day) led to a significant redn. in eosinophil nos. and lung wts. in the mouse model.

Histol. examn. of lungs confirmed the anti-inflammatory effect. E64 greatly reduced ovalbumin-specific T cell nos. in the lymph nodes draining the lung following intranasal challenge while an accumulation of these T cells was found in the "priming" lymph nodes. An anal. of various cells involved in lymphocyte priming and migration revealed that monocytes, ***dendritic*** cells and endothelial cells express high levels of membrane-assocd. cathepsin B activity. Conclusions: Since E64 is not cell permeable and does not inhibit antigen-induced T cell proliferation in vitro or in vivo, the data indicate that membrane-assocd. cysteine proteases, possibly cathepsin B, may regulate T lymphocyte migration in vivo.

L14 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2001:300733 Document No. 134:322694 An extracellular serine protease TADG-15 overexpressed in carcinomas and uses of TADG-15 in diagnosis, treatment and prevention of cancer. O'brien, Timothy J.; Tanimoto, Hirotoshi (The Board of Trustees of the University of Arkansas, USA). PCT Int. Appl. WO 2001029056 A1 20010426, 130 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US29095 20001020. PRIORITY: US 1999-421213 19991020.

AB The present invention provides cDNA encoding a TADG-15 (tumor antigen-derived gene 15) serine ***protease*** from ***human*** that is overexpressed in ovarian tumors. TADG-15 appears to be a transmembrane multidomain serine protease. The TADG-15 cDNA is 3147 base pairs long encoding for a 855 amino acid protein. Also provided is a vector capable of expressing the DNA of the present invention adapted for expression in a recombinant cell and regulatory elements necessary for expression of the DNA in the cell. The present invention further provides for methods of inhibiting TADG-15 expression and/or protease activity, methods of detecting TADG-15 mRNA and/or protein and methods of screening for TADG-15 inhibitors. Addnl., the present invention provides for cell-specific targeting via TADG-15 and methods of vaccinating an individual against TADG-15. The methods described are useful in the diagnosis, treatment and prevention of cancer, particularly breast and ovarian cancer.

L14 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2000:772489 Document No. 133:355232 Enzymatically activated polymeric drug conjugates. Pachence, James M.; Belinka, Benjamin A.; Ramani, Thulasi (Veritas Medical Technologies, Inc., USA). PCT Int. Appl. WO 2000064486 A2 20001102, 100 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US11670 20000428. PRIORITY: US 1999-PV131404 19990428; US 1999-PV163090 19991102.

AB The present invention relates to a polymeric drug conjugate with one or more biol. active agents conjugated via an enzymically cleavable linker to either a regular repeating linear unit comprising a water sol. polymer segment and a multifunctional chem. moiety, or a branched polymer comprising two or more water sol. polymer segments each bound to a common multifunctional chem. moiety, as well as to methods of making such conjugates. The present invention is also directed to pharmaceutical compns. comprising such conjugates and to the use of such conjugates to treat pathol. conditions. A conjugate consisting of Fmoc-doxorubicin-14-O-hemiglutarate deriv. as an active agent, tetrapeptide Val-Gly-Pro-Ala as an enzymically cleaved linker, a multifunctional chem. moiety prepd. from N-fluorenylmethoxycarbonyl-O-tert-butylserine, N-(benzyloxycarbonyl)-ethane-1,2-diamine, and tetrahydropyranyl ether, and polyethylene glycol 2000 was prepd.

L14 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

2000:769004 Document No. 133:319056 Nucleic acids encoding human proteinases and related reagents. Balasubramanian, Sriram; Ford, John; Gorman, Daniel M.; Zurawski, Gerard (Schering Corporation, USA). U.S. US 6140098 A 20001031, 35 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-706216 19960830.

AB Nucleic acids encoding 3 human proteins which exhibit structural properties of motifs characteristic of proteinases, reagents related thereto, including specific antibodies, and purified proteins are described. ***Human*** ***protease*** APG04 is a carboxypeptidase H domain-contg. protein isolated from CDa+ CD34+ ***dendritic*** cells. FHD02, also isolated from ***dendritic*** cells, exhibits amino acid homol. to several hemoglobinases of some parasites and proteases from various seeds or fruits. D1B2 is the human homolog of a mouse antigen designated mouse MS2; the extracellular domain contains a clear metalloproteinase domain related to a family of several well characterized snake venom proteins which seem to inhibit blood clotting processes. Methods of using said reagents and related diagnostic kits are also provided.

L14 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

1998:25937 Document No. 128:254487 Polymerase chain reaction-based identification of a novel serpin from human ***dendritic*** cells. Mueller, Chris G. F.; Ho, Steve; Massacrier, Catherine; Lebecque, Serge; Liu, Yong Jun (Laboratory Immunological Research, Schering-Plough, Dardilly, F-69571, Fr.). European Journal of Immunology, 27(12), 3130-3134 (English) 1997. CODEN: EJIMAF. ISSN: 0014-2980. Publisher: Wiley-VCH Verlag GmbH.

AB A subtraction library of CD40-stimulated human tonsil ***dendritic*** cells was constructed using a polymerase chain reaction approach adapted for low nos. of cells. From this library a cDNA for a serine protease inhibitor, a serpin, was identified which is absent from monocytes, B cells and T cells but expressed in CD40-activated monocyte- and progenitor cell-generated ***dendritic*** cells. In addn., the serpin is expressed in a lung fibroblast cell line and keratinocytes. Its mRNA is detected only in tonsil and thymus. The serpin described reportedly functions as a megakaryocyte maturation factor in the presence of interleukin (IL)-3 and IL-11. This suggests that ***dendritic*** cells may promote the immune response by protecting IL-3 and IL-11 or other essential proteins from degrdn.

L14 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

1997:246789 Document No. 126:315931 Amyloid precursor proteins protect neurons of transgenic mice against acute and chronic excitotoxic injuries in vivo. Masliah, E.; Westland, C. E.; Rockenstein, E. M.; Abraham, C. R.; Mallory, M.; Veinberg, I.; Sheldon, E.; Mucke, L. (Departments of Neurosciences and Pathology, University of California at San Diego, La Jolla, CA, 92093-0624, USA). Neuroscience (Oxford), 78(1), 135-146 (English) 1997. CODEN: NRSCDN. ISSN: 0306-4522. Publisher: Elsevier.

AB The .beta.-amyloid protein precursor (APP) is well conserved across different species and may fulfill important physiol. functions within the CNS. While high-level neuronal expression of amyloidogenic forms of human APP results in .beta.-amyloid prodn. and neurodegeneration, lower levels of neuronal human APP expression in neurons of transgenic mice may primarily accentuate physiol. functions of this mol. To assess the neuroprotective potential of human APP in vivo, mice from seven distinct transgenic lines expressing different human APP isoforms from the neuron-specific enolase promoter were challenged with systemic kainate injections or transgene-mediated glial expression of gp120, an HIV-1 protein capable of inducing excitotoxic neuronal damage. To quantitate human APP-mediated neuroprotection, the area of neuropil occupied by presynaptic terminals and neuronal dendrites in the neocortex and hippocampus of each mouse was detd. using laser scanning confocal microscopy of double-immunolabeled brain sections and computer-aided image anal. Compared with gp120 singly transgenic controls, mice from three of three human APP751/gp120 bigenic lines expressing the 751 amino acid form of human APP at low levels showed significant protection against degeneration of presynaptic terminals; two of these lines also showed significantly less damage to neuronal dendrites. Two of three human APP695/gp120 bigenic lines expressing human APP695 at low levels were protected against presynaptic and ***dendritic*** damage, whereas one low expressor line and a human APP695/gp120 bigenic line expressing human

APP695 at higher levels showed no significant protection. In the corresponding human APP singly transgenic lines, overexpressing only specific human APP isoforms, significant protection against kainate-induced degeneration of presynaptic terminals and neuronal dendrites was found in two of three human APP751 lines and not in any of the four human APP695 lines tested. These results indicate that human APP can protect neurons against chronic and acute excitotoxic insults in vivo and that human APP isoforms differ in their neuroprotective potential, at least with respect to specific forms of neural injury. It is therefore possible that impairments of neuroprotective human APP functions or aberrant shifts in human APP isoform ratios could contribute to neurodegeneration.

L14 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
1996:52728 Document No. 124:106631 Multirepresentation of a peptide analog of the DPPIV (dipeptidyl peptidase IV) substrate, especially of the KPR type, to inhibit the entry of HIV in cells. Hovanessian, Ara; Callebaut, Christian; Krust, Bernard; Jacotot, Etienne; Muller, Sylviane; Briand, Jean-paul; Guichard, Gilles (Institut Pasteur, Fr.). PCT Int. Appl. WO 9529190 A1 19951102, 46 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, NZ; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (French). CODEN: PIXXD2. APPLICATION: WO 1995-FR528 19950421. PRIORITY: FR 1994-4895 19940422.
AB Mols. are disclosed which have a plurality of repeat patterns, esp. of the KPR type, which are recognizable by an ectoprotein (on the cell surface), in particular by the CD26 receptor (also known as the DPPIV enzyme). The peptide patterns are all carried by a peptide matrix enabling their multiple presentation to the enzyme and having an affinity for the latter. The mols. of the invention are the active ingredient of a compn. inhibiting the entry of HIV in cells, in particular for the treatment of a retrovirus-induced infection.

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=> S ENDOMETRIUM
         11483 ENDOMETRIUM
            22 ENDOMETRIUMS
           425 ENDOMETRIA
L15      11531 ENDOMETRIUM
                (ENDOMETRIUM OR ENDOMETRIUMS OR ENDOMETRIA)

=> S L5 AND L15
L16         34 L5 AND L15

=> S L16 NOT (L7,L9,L11,L14)
L17         33 L16 NOT ((L7 OR L9 OR L11 OR L14))

=> D 1-34 CBIB ABS
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L17 ANSWER 1 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2003:795868 Distribution of the serine ***protease*** HtrA1 in normal ***human*** tissues. De Luca, Antonio; De Falco, Maria; Severino, Anna; Campioni, Mara; Santini, Daniele; Baldi, Feliciano; Paggi, Marco G.; Baldi, Alfonso (Department of Medicine and Public Health, Section of Clinical Anatomy, Second University of Naples, Naples, Italy). Journal of Histochemistry and Cytochemistry, 51(10), 1279-1284 (English) 2003. CODEN: JHCYAS. ISSN: 0022-1554. Publisher: Histochemical Society, Inc..
AB The ***human*** HtrA family of ***proteases*** consists of three members:. HtrA2, and. In bacteria, the chief role of HtrA is recognition and degrdn. of misfolded proteins in the periplasm, combining a dual activity of chaperone and protease. In humans, the three HtrA homologues appear to be involved in diverse functions such as cell growth, apoptosis, allergic reactions, fertilization, control of blood pressure, and blood clotting. Previous studies using RNA blot hybridization have shown that the expression of HtrA1 is ubiquitous in normal human tissues. Here we show by immunohistochem. (IHC) that HtrA1 is widely expressed, although different tissue distributions and/or levels of expression were detected in the different tissues examd. In particular, high to medium HtrA1 expression was detected in mature layers of epidermis, in secretory breast epithelium, in liver, and in kidney tubules of cortex, in concordance with its secretory properties. Furthermore, we show a higher protein expression level in the epithelium of proliferative ***endometrium*** ,

in contrast to epithelium of secretory ***endometrium*** , which is almost completely neg. for this protein. This suggests a possible role for HtrA1 in the modulation of tissue activity in this organ. The various expression levels in human tissues indicate several possible roles for HtrA1 in different cell types.

L17 ANSWER 2 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2003:408295 Document No. 139:131039 Complex regulation of decidualization: a role for cytokines and proteases-a review. Salamonsen, L. A.; Dimitriadis, E.; Jones, R. L.; Nie, G. (Prince Henry's Institute of Medical Research, Clayton, Victoria, 3168, Australia). Trophoblast Research, 17(Clinical Complications In Pregnancy), S76-S85 (English) 2003. CODEN: TRREEN. ISSN: 0891-9925. Publisher: Elsevier Science B.V..
AB A review. Decidualization of the endometrial stroma is a precondition for successful establishment of pregnancy. While the local mol. mechanisms driving decidualization are still largely unknown, a no. of autocrine/paracrine factors have been identified as differentiation factors in this process. These include the cytokines, interleukin 11, activin A and monoclonal non-specific suppressor factor .beta. (MNSF.beta.). Furthermore, locally produced proteases, including proprotein convertase 6 and matrix metalloproteinases, enable expansion of the tissue and processing of regulatory mols. This article reviews recent work from the authors' lab. on the roles of these factors in decidualization.

L17 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2003:270227 Document No. 138:266968 Gene expression profiles useful in methods of diagnosis of cancer compositions and methods of screening for modulators of cancer. Afar, Daniel; Aziz, Natasha; Gish, Kurt C.; Hevezi, Peter A.; Mack, David H.; Wilson, Keith E.; Zlotnik, Albert (EOS Biotechnology, Inc., USA). PCT Int. Appl. WO 2003025138 A2 20030327, 767 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-XH29560 20020917. PRIORITY: US 2001-PV323469 20010917; US 2001-PV323887 20010920; US 2001-PV350666 20011113; US 2002-PV355145 20020208; US 2002-PV355257 20020208; US 2002-PV372246 20020412; WO 2002-US29560 20020917.
AB Described herein are genes whose expression are up-regulated or down-regulated in specific cancers, including acute lymphocytic leukemia, glioblastoma, glioblastoma multiforme, glioma, kidney cancer, stomach cancer, melanoma, and benign NEVI. Mol. profiles of various normal and cancerous tissues were detd. and analyzed using the Affymetrix/Eos Hu01 and Hu03 GeneChip microarrays contg. 35,403 and 59,680 probe sets, resp. Related methods and compns. that can be used for diagnosis and treatment of those cancers are disclosed. Also described herein are methods that can be used to identify modulators of selected cancers. [This abstr. record is one of nine records for this documents necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L17 ANSWER 4 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2003:270226 Document No. 138:266967 Gene expression profiles useful in methods of diagnosis of cancer compositions and methods of screening for modulators of cancer. Afar, Daniel; Aziz, Natasha; Gish, Kurt C.; Hevezi, Peter A.; Mack, David H.; Wilson, Keith E.; Zlotnik, Albert (EOS Biotechnology, Inc., USA). PCT Int. Appl. WO 2003025138 A2 20030327, 767 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-XG29560 20020917. PRIORITY: US

2001-PV323469 20010917; US 2001-PV323887 20010920; US 2001-PV350666 20011113; US 2002-PV355145 20020208; US 2002-PV355257 20020208; US 2002-PV372246 20020412; WO 2002-US29560 20020917.

AB Described herein are genes whose expression are up-regulated or down-regulated in specific cancers, including acute lymphocytic leukemia, glioblastoma, glioblastoma multiforme, glioma, kidney cancer, stomach cancer, melanoma, and benign NEVI. Mol. profiles of various normal and cancerous tissues were detd. and analyzed using the Affymetrix/Eos Hu01 and Hu03 GeneChip microarrays contg. 35,403 and 59,680 probe sets, resp. Related methods and compns. that can be used for diagnosis and treatment of those cancers are disclosed. Also described herein are methods that can be used to identify modulators of selected cancers. [This abstr. record is one of nine records for this documents necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L17 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

2003:270225 Document No. 138:266966 Gene expression profiles useful in methods of diagnosis of cancer compositions and methods of screening for modulators of cancer. Afar, Daniel; Aziz, Natasha; Gish, Kurt C.; Hevezi, Peter A.; Mack, David H.; Wilson, Keith E.; Zlotnik, Albert (EOS Biotechnology, Inc., USA). PCT Int. Appl. WO 2003025138 A2 20030327, 767 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-XF29560 20020917. PRIORITY: US 2001-PV323469 20010917; US 2001-PV323887 20010920; US 2001-PV350666 20011113; US 2002-PV355145 20020208; US 2002-PV355257 20020208; US 2002-PV372246 20020412; WO 2002-US29560 20020917.

AB Described herein are genes whose expression are up-regulated or down-regulated in specific cancers, including acute lymphocytic leukemia, glioblastoma, glioblastoma multiforme, glioma, kidney cancer, stomach cancer, melanoma, and benign NEVI. Mol. profiles of various normal and cancerous tissues were detd. and analyzed using the Affymetrix/Eos Hu01 and Hu03 GeneChip microarrays contg. 35,403 and 59,680 probe sets, resp. Related methods and compns. that can be used for diagnosis and treatment of those cancers are disclosed. Also described herein are methods that can be used to identify modulators of selected cancers. [This abstr. record is one of nine records for this documents necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L17 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

2003:270223 Document No. 138:266964 Gene expression profiles useful in methods of diagnosis of cancer compositions and methods of screening for modulators of cancer. Afar, Daniel; Aziz, Natasha; Gish, Kurt C.; Hevezi, Peter A.; Mack, David H.; Wilson, Keith E.; Zlotnik, Albert (EOS Biotechnology, Inc., USA). PCT Int. Appl. WO 2003025138 A2 20030327, 767 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-XD29560 20020917. PRIORITY: US 2001-PV323469 20010917; US 2001-PV323887 20010920; US 2001-PV350666 20011113; US 2002-PV355145 20020208; US 2002-PV355257 20020208; US 2002-PV372246 20020412; WO 2002-US29560 20020917.

AB Described herein are genes whose expression are up-regulated or down-regulated in specific cancers, including acute lymphocytic leukemia, glioblastoma, glioblastoma multiforme, glioma, kidney cancer, stomach cancer, melanoma, and benign NEVI. Mol. profiles of various normal and cancerous tissues were detd. and analyzed using the Affymetrix/Eos Hu01 and Hu03 GeneChip microarrays contg. 35,403 and 59,680 probe sets, resp.

Related methods and compns. that can be used for diagnosis and treatment of those cancers are disclosed. Also described herein are methods that can be used to identify modulators of selected cancers. [This abstr. record is one of nine records for this documents necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L17 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2003:270222 Document No. 138:266963 Gene expression profiles useful in methods of diagnosis of cancer compositions and methods of screening for modulators of cancer. Afar, Daniel; Aziz, Natasha; Gish, Kurt C.; Hevezi, Peter A.; Mack, David H.; Wilson, Keith E.; Zlotnik, Albert (EOS Biotechnology, Inc., USA). PCT Int. Appl. WO 2003025138 A2 20030327, 767 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-XC29560 20020917. PRIORITY: US 2001-PV323469 20010917; US 2001-PV323887 20010920; US 2001-PV350666 20011113; US 2002-PV355145 20020208; US 2002-PV355257 20020208; US 2002-PV372246 20020412; WO 2002-US29560 20020917.
AB Described herein are genes whose expression are up-regulated or down-regulated in specific cancers, including acute lymphocytic leukemia, glioblastoma, glioblastoma multiforme, glioma, kidney cancer, stomach cancer, melanoma, and benign NEVI. Mol. profiles of various normal and cancerous tissues were detd. and analyzed using the Affymetrix/Eos Hu01 and Hu03 GeneChip microarrays contg. 35,403 and 59,680 probe sets, resp. Related methods and compns. that can be used for diagnosis and treatment of those cancers are disclosed. Also described herein are methods that can be used to identify modulators of selected cancers. [This abstr. record is one of nine records for this documents necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L17 ANSWER 8 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2003:242673 Document No. 139:4580 Dipeptidyl peptidase IV expression in endometrial endometrioid adenocarcinoma and its inverse correlation with tumor grade. Khin, Ei Ei; Kikkawa, Fumitaka; Ino, Kazuhiko; Kajiyama, Hiroaki; Suzuki, Takahiro; Shibata, Kiyosumi; Tamakoshi, Koji; Nagasaka, Tetsuro; Mizutani, Shigehiko (Dep. Obstetrics and Gynecol., Nagoya Univ. Hosp., Nagoya, 466-8550, Japan). American Journal of Obstetrics and Gynecology, 188(3), 670-676 (English) 2003. CODEN: AJOGAH. ISSN: 0002-9378. Publisher: Mosby, Inc..
AB Dipeptidyl peptidase IV (DPPIV)/CD26 is a cell surface aminopeptidase. This study investigated the expression and localization of DPPIV in endometrial endometrioid adenocarcinomas of different grades. Immunohistochem. anal. was performed by DPPIV and regulated on activation, normal T-cell expressed and secreted (RANTES) specific monoclonal antibodies. Cell proliferation was evaluated by bromodeoxyuridine (BrdU) uptake assay. Immunohistochem. analyses showed that DPPIV was strongly or moderately stained in glandular cells of the normal secretory phase. In endometrial adenocarcinoma, the DPPIV expression decreased with advancing grade ($P < .01$). Furthermore, RANTES, one of the possible DPPIV substrates, was highly expressed in all grades of endometrial adenocarcinoma cells. The addn. of RANTES to endometrial adenocarcinoma cells increased proliferation in a concn.-dependent manner. Conclusion: DPPIV is expressed in normal endometrial glandular cells, but its expression in endometrial adenocarcinoma is down-regulated with increasing grade. These data also suggest a regulatory role of this ectoenzyme in neoplastic transformation and progression of endometrial adenocarcinomas possibly by degrading certain bioactive peptides such as RANTES.

L17 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2003:117862 Document No. 138:183113 Cloning, sequence, expression and therapeutic and drug screening use of a pregnancy-related serine ***protease*** from ***human*** and mouse. Nie, Guiying; Salamonsen, Lois Adrienne; Li, Ying; Hampton, Anne Lorraine; Findlay, John

Kerr (Prince Henry's Institute of Medical Research, Australia). PCT Int. Appl. WO 2003011905 A1 20030213, 159 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-AU1010 20020730. PRIORITY: AU 2001-6707 20010730.

AB The invention relates to a enzyme predicted to be a serine protease, which is specifically expressed in assocn. with embryo implantation and placentation in pregnant uterus. The serine protease has an IGF-binding motif. The serine protease of the invention is referred to as pregnancy-related serine protease (PRSP). The cDNA sequences and the encoded amino acid sequences of long and short isoenzymes of the pregnancy-related serine protease are disclosed. The enzyme of the invention is useful in the evaluation of fertility and monitoring of early pregnancy, placental development and function, fetal development, parturition, and conditions such as pre-eclampsia, intrauterine growth restriction, early abortion, abnormal uterine bleeding, endometriosis, and cancers, and may provide a potential target for contraception. It may also be important in diseases of the heart, testis or ovary, and may play a role in muscle function, including cardiac muscle, skeletal muscle, lung and the diaphragm. In addn. the enzyme of the invention is useful in the screening of candidate drugs for fertility control or for treatment of fertility-related disorders.

L17 ANSWER 10 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

2002:939998 Document No. 138:281304 Protease activated receptor-1 is down regulated by levonorgestrel in endometrial stromal cells. Hague, S.; Oehler, M. K.; MacKenzie, I. Z.; Bicknell, R.; Rees, M. C. P. (Nuffield Department of Obstetrics and Gynaecology, Univ. Oxford, Oxford, OX3 9DU, UK). Angiogenesis, 5(1-2), 93-98 (English) 2002. CODEN: AGIOFT. ISSN: 0969-6970. Publisher: Kluwer Academic Publishers.

AB Progestogens are used clin. for contraception, to control excessive menstrual bleeding and to oppose estrogen in hormone replacement therapy. The use of intrauterine levonorgestrel (LNG) is however, assocd. with endometrial atrophy and decidualization of the stroma. In this study, the authors aimed to identify genes whose expression is modulated by LNG either alone or in combination with progesterone. Thus endometrial stromal cells were stimulated with progesterone, LNG or LNG and progesterone. Poly-A RNA was isolated and used to probe expression arrays. The expression of a no. of genes was altered on exposure to LNG or LNG and progesterone. Alteration of expression patterns was confirmed using semi-quant. RT-PCR and western blot anal. In particular, the protease activated receptor-1 (PAR-1) gene that encodes a receptor for thrombin was down regulated. This is the first demonstration that PAR-1 is down regulated by the progestogen LNG in human ***endometrium*** . Alteration in the expression levels of this receptor may affect both growth and hemostatic activity within the ***endometrium*** and may account for the obsd. morphol. effects seen in users of intrauterine LNG delivery devices.

L17 ANSWER 11 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

2002:715289 Document No. 138:86972 Human kallikrein 10 expression in normal tissues by immunohistochemistry. Petraki, Constantina D.; Karavana, Vassiliki N.; Luo, Liu-Ying; Diamandis, Eleftherios P. (Department of Pathology, Evangelismos Hospital, Athens, Greece). Journal of Histochemistry and Cytochemistry, 50(9), 1247-1261 (English) 2002. CODEN: JHCYAS. ISSN: 0022-1554. Publisher: Histochemical Society, Inc..

AB The normal epithelial cell-specific 1 (NES1) gene (official name kallikrein gene 10, KLK10) was recently cloned and encodes for a putative secreted serine ***protease*** (***human*** kallikrein 10, hK10). Several studies have confirmed that hK10 shares many similarities with the other kallikrein members at the DNA, mRNA, and protein levels. The enzyme was found in biol. fluids, tissue exts., and serum. Here we report the first detailed immunohistochem. (IHC) localization of hK10 in normal human tissues. We used the streptavidin-biotin method with two hK10-specific antibodies, a polyclonal rabbit and a monoclonal mouse antibody, developed

in house. We analyzed 184 paraffin blocks from archival, current, and autopsy material, prepd. from almost every normal human tissue. The staining pattern, the distribution of the immunostaining, and its intensity were studied in detail. Previously, we reported the expression of another novel human kallikrein, hK6, by using similar techniques. The IHC expression of hK10 was generally cytoplasmic and not organ-specific. A variety of normal human tissues expressed the protein. Glandular epithelia constituted the main immunoexpression sites, with representative organs being the breast, prostate, kidney, epididymis, ***endometrium*** , fallopian tubes, gastrointestinal tract, bronchus, salivary glands, bile ducts, and gallbladder. The choroid plexus epithelium, the peripheral nerves, and some neuroendocrine organs (including the islets of Langerhans, cells of the adenohypophysis, the adrenal medulla, and Leydig cells) expressed the protein strongly and diffusely. The spermatic epithelium of the testis expressed the protein moderately. A characteristic immunostaining was obsd. in Hassall's corpuscles of the thymus, oxyphilic cells of the thyroid and parathyroid glands, and chondrocytes. Comparing these results with those of hK6, we obsd. that both kallikreins had a similar IHC expression pattern.

L17 ANSWER 12 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

2002:646213 Document No. 137:367099 Secretory leukocyte ***protease*** inhibitor mediates proliferation of ***human*** endometrial epithelial cells by positive and negative regulation of growth-associated genes. Zhang, Daying; Simmen, Rosalia C. M.; Michel, Frank J.; Zhao, Ge; Vale-Cruz, Dustin; Simmen, Frank A. (Interdisciplinary Concentration in Animal Molecular & Cell Biology and the Department of Animal Sciences, University of Florida, Gainesville, FL, 32611-0910, USA). Journal of Biological Chemistry, 277(33), 29999-30008 (English) 2002. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB Secretory leukocyte protease inhibitor (SLPI) inhibits chymotrypsin, trypsin, elastase, and cathepsin G. This protein also exhibits proliferative effects, although little is known about the mol. mechanisms underlying this activity. We have generated SLPI-ablated epithelial sublines by stably transfecting the Ishikawa human endometrial cell line with an antisense human SLPI RNA expression vector. We demonstrate a pos. correlation between cellular SLPI prodn. and proliferation. We further show that Ishikawa sublines expressing low to undetectable SLPI have correspondingly increased and decreased expression, resp., of transforming growth factor-.beta.1 and cyclin D1 genes, relative to parental cells. SLPI selectively increased cyclin D1 gene expression, with the effect occurring in part at the level of promoter activity. Cellular SLPI levels neg. influenced the anti-proliferative and pro-apoptotic insulin-like growth factor-binding protein-3 expression. We also identified lysyl oxidase, a phenotypic inhibitor of the ras oncogenic pathway and a tumor suppressor, as SLPI-repressed gene, whose expression is up-regulated by transforming growth factor-.beta.1. Our results suggest that SLPI acts at the node(s) of at least three major interacting growth inhibitory pathways. Because expression of SLPI is generally high in epithelial cells exhibiting abnormal proliferation such as in carcinomas, SLPI may define a novel pathway by which cellular growth is modulated.

L17 ANSWER 13 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

2002:533683 Document No. 138:36432 Proteases at the endometrial-trophoblast interface: Their role in implantation. Salamonsen, Lois A.; Nie, Guiying (Prince Henry's Institute of Medical Research, Clayton, 3168, Australia). Reviews in Endocrine & Metabolic Disorders, 3(2), 133-143 (English) 2002. CODEN: REMDCG. ISSN: 1389-9155. Publisher: Kluwer Academic Publishers.

AB A review focuses on the contribution of proteases, such as matrix metalloproteinases, cysteine and serine proteases in implantation. Matrix-degrading enzymes are important for the invasive events of implantation and subsequent placentation. The effects of genetic manipulation of protease or related genes on the implantation process are considered.

L17 ANSWER 14 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

2002:493378 Document No. 137:382602 Effect of menstrual status on antibacterial activity and secretory leukocyte ***protease*** inhibitor production by ***human*** uterine epithelial cells in culture. Fahey, John V.; Wira, Charles R. (Department of Physiology,

Dartmouth Medical School, New Hampshire, Lebanon). Journal of Infectious Diseases, 185(11), 1606-1613 (English) 2002. CODEN: JIDIAQ. ISSN: 0022-1899. Publisher: University of Chicago Press.

AB The objective of this study was to examine the prodn. of antibacterial factor(s) by uterine epithelial cells from pre- and postmenopausal women. Apical rinses from polarized epithelial cells recovered from women at the proliferative and secretory stages of the menstrual cycle were equally effective in killing Staphylococcus aureus and Escherichia coli, but those from postmenopausal women were not. Secretory leukocyte protease inhibitor (SLPI) concns. of apical washes from premenopausal women were significantly higher than those obtained from postmenopausal women. SLPI prodn. correlated with bactericidal activity with respect to menstrual status and time in culture. Anti-SLPI antibody significantly decreased bactericidal activity of premenopausal epithelial cell rinses. The endometrial epithelial cell line HEC-1A did not have a bactericidal effect, nor did it produce SLPI. In contrast, HEC-1B cells produced SLPI and a factor that inhibited bacterial growth. These results indicate that menstrual status (pre- vs. postmenopausal) influences the prodn. of SLPI and bactericidal activity by uterine epithelial cells.

L17 ANSWER 15 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

2002:355307 Document No. 137:152861 Identification and regulation of the IGFBP-4 protease and its physiological inhibitor in human trophoblasts and endometrial stroma: Evidence for paracrine regulation of IGF-II bioavailability in the placental bed during human implantation. Giudice, L. C.; Conover, C. A.; Bale, L.; Faessen, G. H.; Ilg, K.; Sun, I.; Imani, B.; Suen, L.-F.; Irwin, J. C.; Christiansen, M.; Overgaard, M. T.; Oxvig, C. (Department of Gynecology and Obstetrics, Stanford University Medical Center, Stanford, CA, 94305, USA). Journal of Clinical Endocrinology and Metabolism, 87(5), 2359-2366 (English) 2002. CODEN: JCEMAZ. ISSN: 0021-972X. Publisher: Endocrine Society.

AB The IGF family plays an important role in implantation and placental physiol. IGF-II is abundantly expressed by placental trophoblasts, and IGF binding protein (IGFBP)-4, a potent inhibitor of IGF actions, is the second most abundant IGFBP in the placental bed, expressed exclusively by the maternal decidua. Proteolysis of IGFBP-4 results in decreased affinity for IGF peptides, thereby enhancing IGF actions. In the current study, we have identified the IGFBP-4 ***protease*** and its inhibitor in ***human*** trophoblast and decidualized endometrial stromal cell cultures, and we have investigated their regulation in an effort to understand control of IGF-II bioavailability at the placental-decidual interface in human implantation. IGFBP-4 protease activity was detected in conditioned media (CM) from human trophoblasts and decidualized endometrial stromal cells using 125I-IGFBP-4 substrate. Identification of the IGFBP-4 protease as pregnancy-assocd. plasma protein-A (PAPP-A) was confirmed by specific immunoinhibition and immunodepletion of the IGFBP-4 protease activity with specific PAPP-A antibodies. The IGFBP-4 protease activity was IGF-II-dependent in trophoblast CM. In decidualized stromal CM, PAPP-A/IGFBP-4 protease activity was also IGF-II-dependent, but was evident only when IGF-II was added in molar excess of the predominant IGFBP in decidualized stromal cell CM, IGFBP-1, supporting bioavailable IGF-II as a key cofactor of IGFBP-4 proteolysis by PAPP-A. Cultured first and second trimester human trophoblasts (n = 5) secreted PAPP-A into CM with mean .+-. SEM levels of 172.4 .+-. 32.8 mIU/L 105 cells, detd. by specific ELISA. PAPP-A in trophoblast CM (n = 3) and did not change in the presence of IGF-II (1-100 ng/mL). Cultured human endometrial stromal cells (n = 4) secreted low levels of PAPP-A (6.25 .+-. 3.6 mIU/L 105 cells). A physiol. inhibitor of PAPP-A, the proform of eosinophil major basic protein (proMBP), was detected in trophoblast CM at levels of 1853 .+-. 308 mIU/L 105 cells, detd. by specific ELISA, and was nearly undetectable in CM of human endometrial stromal cells. Upon in vitro decidualization of endometrial stromal cells with progesterone, PAPP-A levels in CM increased nearly 9-fold without a concomitant change in proMBP. In contrast to the expts. with trophoblasts, IGF-II and the IGF analogs, Leu27 IGF-II, and Des (1-6) IGF-II, resulted in a dose-dependent decrease of PAPP-A levels in decidualized endometrial stromal CM by 70-90%, and a dose-dependent increase in proMBP of 14- to 41-fold. The data demonstrate conclusively that the IGF-II-dependent IGFBP-4 ***protease*** of ***human*** trophoblast and decidual origin is PAPP-A. Furthermore, the differential regulation of decidual PAPP-A and proMBP by insulin-like peptides supports a role for trophoblast-derived

IGF-II as a paracrine regulator of these maternal decidual products that have the potential to regulate IGF-II bioavailability at the trophoblast-decidual interface. Overall, the data underscore potential roles for a complex family of enzyme (PAPP-A), substrate (IGFBP-4), inhibitor (proMBP), and cofactor (IGF-II) in the placental bed during human implantation.

L17 ANSWER 16 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2002:285562 Document No. 137:61578 Expressed gene sets as markers for specific tumors. Ramaswamy, Sridhar; Golub, Todd B.; Tamayo, Pablo; Angelo, Michael (Whitehead Institute for Biomedical Research, USA; Danna-Farber Cancer Institute, Inc.). PCT Int. Appl. WO 2002024956 A2 20020328, 715 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-XB29287 20010919. PRIORITY: US 2000-PV233534 20000919; US 2001-PV278749 20010326; WO 2001-US29287 20010919.

AB Sets of genetic markers for specific tumor classes are described, as well as methods of identifying a biol. sample based on these markers. Total RNA was isolated from .apprx.300 human tumor and normal tissue specimens representing 30 individual classes of tumor or normal tissue, and cDNA produced using established mol. biol. protocols was hybridized to two high d. Affymetrix oligonucleotide microarrays (Hu6800FL and Hu35KsubA0). Raw expression data was combined into a master data set contg. the expression values for between 6800 and 16,000 genes expressed by each individual sample. A filter was applied to this data set which only allows those genes expressed at 3-fold above baseline and with an abs. difference in expression value of 100 to pass. By comparing the sets of genes which are expressed specifically in one class of tumor (e.g., pancreatic adenocarcinoma) vs. its accompanying normal tissue (e.g., normal pancreas), sets of genes were detd. which are specific to various tumors and their normal tissue counterparts. Also described are diagnostic, prognostic, and therapeutic screening uses for these markers, as well as oligonucleotide arrays comprising these markers. [This abstr. record is one of 4 records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L17 ANSWER 17 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2002:285556 Document No. 137:45438 Expressed gene sets as markers for specific tumors. Ramaswamy, Sridhar; Golub, Todd B.; Tamayo, Pablo; Angelo, Michael (Whitehead Institute for Biomedical Research, USA; Danna-Farber Cancer Institute, Inc.). PCT Int. Appl. WO 2002024956 A2 20020328, 715 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-XA29287 20010919. PRIORITY: US 2000-PV233534 20000919; US 2001-PV278749 20010326; WO 2001-US29287 20010919.

AB Sets of genetic markers for specific tumor classes are described, as well as methods of identifying a biol. sample based on these markers. Total RNA was isolated from .apprx.300 human tumor and normal tissue specimens representing 30 individual classes of tumor or normal tissue, and cDNA produced using established mol. biol. protocols was hybridized to two high d. Affymetrix oligonucleotide microarrays (Hu6800FL and Hu35KsubA0). Raw expression data was combined into a master data set contg. the expression values for between 6800 and 16,000 genes expressed by each individual sample. A filter was applied to this data set which only allows those genes expressed at 3-fold above baseline and with an abs. difference in expression value of 100 to pass. By comparing the sets of genes which are expressed specifically in one class of tumor (e.g., pancreatic adenocarcinoma) vs. its accompanying normal tissue (e.g., normal

pancreas), sets of genes were detd. which are specific to various tumors and their normal tissue counterparts. Also described are diagnostic, prognostic, and therapeutic screening uses for these markers, as well as oligonucleotide arrays comprising these markers. [This abstr. record is one of 4 records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L17 ANSWER 18 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2001:635412 Document No. 135:327735 Aminopeptidase A/angiotensinase: A new cell-surface ***peptidase*** in ***human*** ***endometrium*** . Ando, Hisao; Toda, Shigeru; Tsukahara, Shin-ichiro; Kotani, Yoshiaki; Abe, Harumi; Nomura, Masao; Murata, Yasutaka; Itakura, Atsuo; Nomura, Seiji; Masahashi, Tetsuo; Nagasaka, Tetsuro; Mizutani, Shigehiko (Department of Obstetrics and Gynecology, Nagoya University School of Medicine, Nagoya, 466-8550, Japan). International Congress Series, 1218(Cell-Surface Aminopeptidases: Basic and Clinical Aspects), 203-209 (English) 2001. CODEN: EXMDA4. ISSN: 0531-5131. Publisher: Elsevier Science B.V..
AB Angiotensin II (AngII) is a well-known physiol. substrate of aminopeptidase A (APA, EC 3.4.11.7). AngII is a biol. active peptide acting as a potent vasoconstrictor, angiogenic mediator and growth promoter. APA cleaves N-terminal Asp from AngII and thus inactivates AngII. Immunohistochem. of normal human endometrial specimens obtained from dating biopsy and hysterectomy operations. Cell proliferation anal. with endometrial stromal cell (ESC) culture. In proliferative ***endometrium*** , intense staining was obsd. in the epithelium, while stromal cells showed weak staining. In the secretory phase, APA was negligible in the decidualized stroma, whereas the other stromal region showed distinctive pos. staining. DNA synthesis of cultured ESC increased in response to AngII. In the proliferative phase, AngII may be involved in the proliferation of ESC, up to one-third of which are differential into decidual cells in the secretory phase. Since the decidualization process of ESC starts around the spiral arterioles, high AngII concn. in the decidualized stroma in the absence of APA may increase the vascular permeability. This should have the advantage of supplying the implanted embryo with oxygen and nutrition. However, vasoconstriction may be eventually induced in the high AngII concn. Therefore, the initiation of menstruation can be explained from our results using a similar vasoconstriction theory to that for endothelins and NEP/CD10.

L17 ANSWER 19 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2001:168148 Document No. 134:218930 ***Human*** serine ***protease*** inhibitor headpin and its gene and diagnostic and therapeutic uses. Clayman, Gary L.; Nakashima, Torahiko; Spring, Paul M. (Board of Regents, the University of Texas System, USA). PCT Int. Appl. WO 2001016324 A2 20010308, 213 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US24214 20000831. PRIORITY: US 1999-PV151776 19990831.
AB The present invention describes a novel gene encoding a novel protein termed headpin (for head and neck serpin) that is homologous to known serine protease inhibitors. Headpin is a differentially expressed, novel serine proteinase inhibitor that belongs to the ov-serpin family and demonstrates a hinge region consensus sequence that predicts an inhibitory function. Headpin was cloned from a keratinocyte cDNA library, and its expression pattern by Northern blot anal. indicates that it is most likely produced by keratinizing epithelium. The endogenous expression headpin in normal oral keratinocytes, and its absence or down-regulation in squamous cell carcinoma of the oral cavity, supports the involvement of headpin as a marker for squamous differentiation or a gene disadvantageous to tumor function. Headpin has been grouped into the cluster of serpins located at chromosome 18q21.3/18q22. This region is a known area for loss of heterozygosity and other deletional events often assocd. with head and neck cancer. The invention describes methods and compns. of the nucleic acids, encoded proteins, antibodies, pharmaceuticals, cancer treatments, diagnostics and screens for modulators of headpin.

L17 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
2000:371126 Document No. 134:16448 Secretory leukocyte protease inhibitor inhibits infection of monocytes and lymphocytes with human immunodeficiency virus type 1 but does not interfere with transcytosis of

cell-associated virus across tight epithelial barriers. Hocini, Hakim; Becquart, Pierre; Bouhlal, Hicham; Adle-Biassette, Homa; Kazatchkine, Michel D.; Belec, Laurent (Unite INSERM U430, Hopital Broussais, Paris, 75674, Fr.). Clinical and Diagnostic Laboratory Immunology, 7(3), 515-518 (English) 2000. CODEN: CDIMEN. ISSN: 1071-412X. Publisher: American Society for Microbiology.

AB Here, the authors demonstrate that recombinant ***human*** secretory leukocyte ***protease*** inhibitor (rhSLPI) inhibits infection of lymphocyte- and monocyte-derived tumor cell lines and peripheral blood lymphocytes with lab.-adapted isolates and with the primary isolate, NDK, of free human immunodeficiency virus type 1 (HIV-1). In contrast, rhSLPI did not exhibit inhibitory activity toward transcytosis of cell-assocd. HIV-1 through a tight monolayer of endometrial epithelial cells. Thus, the inhibitory effect of SLPI is restricted to free HIV-1 in corporal fluids.

L17 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

2000:132133 Document No. 132:306165 Presence of secretory leukocyte ***protease*** inhibitor in ***human*** ***endometrium*** and first trimester decidua suggests an antibacterial protective role. King, Anne E.; Critchley, Hilary O. D.; Kelly, Rodney W. (Medical Research Council Reproductive Biology Unit, University of Edinburgh, Edinburgh, EH3 9ET, UK). Molecular Human Reproduction, 6(2), 191-196 (English) 2000. CODEN: MHREFD. ISSN: 1360-9947. Publisher: Oxford University Press.

AB Secretory leukocyte protease inhibitor (SLPI) is a neutrophil elastase inhibitor which also has antibacterial and anti-inflammatory properties. It is found assocd. with mucosal membranes. Although SLPI was reported in the cervix it has not thus far been reported in human ***endometrium*** . This study investigates the presence of SLPI in ***endometrium*** , 1st trimester decidua, and trophoblast. Cultured 1st trimester decidua was found to produce 4.7 ng/mg/24 h of SLPI. ***Endometrium*** and trophoblast were both found to secrete significantly lower amts. of SLPI although endometrial expression was menstrual cycle dependent with increased secretion in the secretory phase. Although relatively low concns. of SLPI were released from the ***endometrium*** during culture, most of the SLPI remained assocd. with the tissue and could be recovered with mild acid extn. This is in agreement with the high isoelec. point (pI) for SLPI, assocd. with high soly. at low pH. The main site of SLPI synthesis in ***endometrium*** and decidua was found to be the glandular epithelium. An antibiotic role for SLPI in the ***endometrium*** and decidua during implantation and pregnancy would be consistent with the expression profile and localization of SLPI.

L17 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

1998:100561 Document No. 128:226459 Human endometrial stromal cells generate uncombined .alpha.-subunit from human chorionic gonadotropin, which can synergize with progesterone to induce decidualization. Nemansky, Martin; Moy, Edmond; Lyons, Curtis D.; Yu, Irene; Blithe, Diana L. (Unit Glycobiology, Developmental Endocrinology Branch, National Inst. Child Health & Human Development, National Inst. Health, Bethesda, MD, 20892, USA). Journal of Clinical Endocrinology and Metabolism, 83(2), 575-581 (English) 1998. CODEN: JCEMAZ. ISSN: 0021-972X. Publisher: Endocrine Society.

AB During the secretory phase of the menstrual cycle, endometrial stromal cells differentiate into decidual cells, which play a crucial role in implantation and maintenance of pregnancy. In this and the authors' previous study, they demonstrate that glycoprotein hormone free .alpha.-subunit potentiates progesterone-mediated decidualization of human endometrial stromal cells in vitro. Although addn. of intact hCG to cultures resulted in stimulatory activity, its potency was 20-fold less than that of .alpha.-subunit. However, in the present study decidualizing endometrial cells actively generate uncombined .alpha.-subunit by dissocg. hCG. The amt. of dissocd. .alpha.-subunit could fully account for the stimulatory activity obsd. with hCG. Active dissocn. of hCG was dependent on the presence of endometrial cells and did not occur in conditioned medium, excluding involvement of a stable secreted factor such as a protease. In addn. to dissocd. .alpha.- and .beta.-subunits, minor amts. of .beta.-core and .alpha.-fragments were detected as degrdn. products during active dissocn. The authors also obsd. an increase in .beta.-immunoreactivity that coeluted with hCG on size-exclusion gel chromatog., indicating that a portion of the still dimeric hCG may have

been nicked in the dissocn. process. However, using an assay with specificity for nicked hCG, the authors showed that dissocn. of hCG was not produced from a pool of preexisting nicked hCG. These findings more firmly established the concept that gonadotropin hormone free .alpha.-subunit plays a role in the regulation of human endometrial cell differentiation. In addn., identification of the various products formed by incubation of hCG with decidualizing cells yielded insight into the mechanism of hCG degrdn., and may explain some activity previously ascribed to hCG.

L17 ANSWER 23 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
1996:512020 Document No. 125:163913 Cell surface ***peptidases*** in ***human*** ***endometrium*** . Imai, Kimitoshi; Kanzaki, Hideharu; Mori, Takahide (Faculty of Medicine, Kyoto University, Kyoto, 606-01, Japan). Molecular Human Reproduction, 2(6), 425-431 (English) 1996. CODEN: MHREFD. ISSN: 1360-9947. Publisher: Oxford University Press.
AB A review with 123 refs. Three cell surface peptidases have been shown to be present in the human ***endometrium*** . Aminopeptidase N and neprilysin (neutral endopeptidase) have been detected on the endometrial stromal cells and decidual cells, whereas dipeptidyl peptidase IV has been detected on the endometrial glandular cells and surface epithelium. As these cell surface peptidases can degrade a variety of biol.-active peptides including cytokines and growth factors, they are considered to be involved in the local metab. of these mols. In addn., recent studies have indicated that they are involved in local immune responses, cell attachment, and cellular maturation/differentiation of endometrial cells, and suggest an important role of these endometrial cell surface peptidases in implantation processes.

L17 ANSWER 24 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
1995:616636 Document No. 123:165603 The expression of peptidase antigens, CD10/neutral endopeptidase, CD13/aminopeptidase N, and CD26/dipeptidyl ***peptidase*** IV in ***human*** ***endometrium*** . Kanzaki, Hideharu; Imai, Kimitoshi; Fujiwara, Hiroshi; Maeda, Michiyuki; Mori, Takahide (Fac. Med., Kyoto Univ., Kyoto, 606-01, Japan). Endocrinol. Embryo-Endometrium Interact., [Proc. Satell. Symp. Ninth Int. Congr. Endocrinol.], Meeting Date 1992, 67-75. Editor(s): Glasser, Stanley R.; Mulholland, Joy; Psychoyos, Alexandre. Plenum: New York, N. Y. (English) 1994. CODEN: 61MZAE.
AB A review with 23 refs. on immunochem. evidence for the presence of neutral endopeptidase, aminopeptidase N, and dipeptidyl ***peptidase*** IV in ***human*** ***endometrium*** .

L17 ANSWER 25 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
1995:392086 Document No. 122:261641 Protease and protease inhibitor expression during in vitro decidualization of human endometrial stromal cells. Schatz, Frederick; Papp, Csaba; Toth-Pal, Erno; Cudemo, Vito; Hausknecht, Virginia; Krikun, Graciela; Markiewicz, Leszek; Gavi, Beni; Wang, En-Yu; et al. (Department Obstetrics, Gynecology and Reproductive Science, Mount Sinai Medical Center, New York, NY, 10029-6574, USA). Annals of the New York Academy of Sciences, 734(Human Endometrium), 33-42 (English) 1994. CODEN: ANYAA9. ISSN: 0077-8923.
AB A review, with 52 refs., of ovarian steroid-regulated protease and ***protease*** inhibitor expression in cultured ***human*** endometrial stromal cells, including the integral role of extracellular matrix turnover in decidualization.

L17 ANSWER 26 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN
1995:223717 Document No. 122:47365 The insulin-like growth factor system in human peritoneal fluid: its effects on endometrial stromal cells and its potential relevance to endometriosis.. Giudice, L. C.; Dsupin, B. A.; Gargosky, S. E.; Rosenfeld, R. G.; Irwin, J. C. (Department of Gynecology and Obstetrics, Stanford University Medical Center, Stanford, CA, 94305, USA). Journal of Clinical Endocrinology and Metabolism, 79(5), 1284-93 (English) 1994. CODEN: JCEMAZ. ISSN: 0021-972X. Publisher: Endocrine Society.
AB Peritoneal fluid (PF) lines the abdomen and pelvis and is believed to contain growth factors that stimulate endometriosis, a benign gynecol. condition assocd. with pelvic pain and infertility, in which endometrial cells proliferate and differentiate on the pelvic peritoneum, outside of their norma local within the uterus. In this study, we examd. the IGF

system in 7 paired samples of PF and serum from normally cycling women and examd. the mitogenic potential of this fluid on cultured endometrial stromal cells. IGF-I, IGF-II, and IGFBP-1, -2, -3, and -4 were identified in PF by immunoassays. PF IGF levels, detd. by RIA, were approx. 60% of paired serum levels, and PF levels of IGFBP-2 and IGFBP-3, detd. by Western ligand blotting and RIA, resp., and were approx. half of their serum concns. IGFBP-4 was barely detectable by Western ligand blotting in PF, and levels of IGFBP-1, detd. by immunoassay, were not appreciably different in PF and serum. Incubation of [125I]IGF-II with serum and PF and subsequent size-exclusion chromatog. at neural pH revealed approx. equal incorporation of radiolabel in the IGFBP regions of 150 and 44 kilodaltons (kDa) in serum and primarily in the 44-kDa region in PF. RIA of IGFBP-3 in the IGFBP regions of column effluent revealed that the majority of IGFBP-3 was in the 150-kDa region in both serum and PF, suggesting the presence of the ternary complex in PF. Western ligand blotting of column effluent samples revealed 37-/43-kDa IGFBP-3 primarily in the 150-kDa complex in serum and a marked redn. in the amt. of the 37-/43-kda IGFBP in PF. Western immunoblotting of column effluent with IGFBP-3 antiserum revealed immunoreactive IGFBP-3 forms of 37-43 kDa (major) and 28 kDa (minor) in serum and almost exclusively the 28-kDa band in PF, suggesting that IGFBP-3 in PF may be proteolytically processed. The presence of an IGFBP-3 protease was confirmed using [125I]IGFBP-3 as substrate and was not appreciably present in paired serum samples. Inhibitor profiles demonstrated that this protease is a metal-independent serine protease, and its approx. relative mol. mass was 69 kDa, detd. as detd. by size-exclusion chromatog. The mitogenic potential of IGF peptides and PF was assessed on cultured endometrial stromal cells to test the hypothesis that IGFs in PF may stimulate the growth of ***endometrium*** in the pelvic cavity, for example in the disorder of endometriosis. IGF-I and IGF-II were mitogenic to endometrial stromal cells, and max. growth stimulation occurred at 10 and 50 ng/mL, resp. PF was also mitogenic to endometrial stromal cells in a dose-dependent fashion, and this mitogenic effect was inhibited up to 30% in the presence of .alpha.IR3, a blocking antibody to the type I IGF receptor. These data demonstrate that the IGF system (IGF peptides, IGFBPs, and an IGFBP ***protease***) is present in ***human*** PF. Furthermore, they suggest that the IGF system may be one of several growth factor systems in PF that has the capacity to stimulate endometrial cellular proliferation and may participate in the growth of ectopic ***endometrium*** on the pelvic peritoneum, as in the disorder of endometriosis.

L17 ANSWER 27 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

1994:692851 Document No. 121:292851 Insulin-like growth factors (IGFs), IGF binding proteins (IGFBPs) and IGFBP ***protease*** in ***human*** uterine ***endometrium*** : Their potential relevance to endometrial cyclic function and maternal-embryonic interactions. Giudice, L. C.; Irwin, J. C.; Dsupin, B. A.; de las Fuentes, L.; Jin, I. H.; Vu, T. H.; Hoffman, A. R. (Department Gynecology and Obstetrics, Stanford University Medical Center, Stanford, CA, 94305, USA). International Congress Series, 1056(INSULIN-LIKE GROWTH FACTORS AND THEIR REGULATORY PROTEINS), 351-61 (English) 1994. CODEN: EXMDA4. ISSN: 0531-5131.

AB A review, with 35 refs., of IGF, IGFBP and IGF receptor gene expression in human ***endometrium*** as well as the stromal response to IGF peptides and the secretion of a novel IGFBP-4 protease by endometrial stromal cells.

L17 ANSWER 28 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

1994:601660 Document No. 121:201660 Bestatin, a potent aminopeptidase-N inhibitor, inhibits in vitro decidualization of human endometrial stromal cells. Inoue, Takuya; Kanzaki, Hideharu; Imai, Kimitoshi; Narukawa, Shinji; Higuchi, Toshihiro; Katsuragawa, Hiroshi; Maeda, Michiyuki; Mori, Takahide (Faculty of Medicine, Kyoto University, Kyoto, 606-01, Japan). Journal of Clinical Endocrinology and Metabolism, 79(1), 171-5 (English) 1994. CODEN: JCEMAZ. ISSN: 0021-972X.

AB We have reported that human endometrial stromal cells (ESC) express a cluster of differentiation-13 antigen/aminopeptidase-N, and the expression of this peptidase antigen was shown to increase with the decidualization of ESC. To clarify the role of this ***peptidase*** in ***human*** ***endometrium*** , the effect of bestatin ([(2S,3R)-3-amino-2-hydroxy-4-phenylbutanoyl]-(S)-leucine), an inhibitor of aminopeptidase-N, on the decidualization of ESC in vitro was examd. Purified human ESC were

cultured for 12 days in the presence of 10-6 mol/L progesterone with or without bestatin. Decidualization was assessed by PRL prodn. and morphol. transformation. The effects of a stereoisomer of bestatin and of pepstatin were similarly examd. using the same culture system. Bestatin inhibited progesterone-induced PRL prodn. in a dose-dependent manner, with no effect on cell no. or viability, whereas neither its stereoisomer nor pepstatin inhibited aminopeptidase activity or PRL prodn. The morphol. transformation of ESC was also inhibited by bestatin, but not by its stereoisomer or pepstatin. These findings demonstrate that the inhibition of aminopeptidase-N activity blocks the in vitro decidualization of ESC and suggest an important role for this peptidase in the functional differentiation of human ESC.

L17 ANSWER 29 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

1993:486539 Document No. 119:86539 Gonadotropin-mediated inhibition of proteolytic enzymes produced by human trophoblast in culture. Milwidsky, Ariel; Finci-Yeheskel, Zvezdana; Yagel, Simcha; Mayer, Michael (Dep. Obstetr., Hadassah Hosp. Mount Scopus, Jerusalem, 91240, Israel). Journal of Clinical Endocrinology and Metabolism, 76(5), 1101-5 (English) 1993. CODEN: JCEMAZ. ISSN: 0021-972X.

AB The effect of gonadotropins on proteases that were suggested to be implicated in the invasive activity of the trophoblast was investigated. Human chorionic gonadotropin (hCG) levels ranging from 10 .times. 103 to 333 .times. 103 IU/L produced a dose-dependent inhibition of the in vitro globinolytic activity of the purified proteases trypsin, chymotrypsin, and urokinase, but failed to inhibit plasmin, collagenase, elastase, and tissue-type plasminogen activator. Likewise, FSH inhibited purified trypsin and urokinase, but not plasmin or tissue-type plasminogen activator. Culture medium conditioned with ***human*** trophoblast displayed serine ***protease*** and urokinase-like activities; exposure of the cultured trophoblast to exogenous hCG markedly suppressed serine protease and urokinase activities in the conditioned medium. A short treatment of the conditioned medium with trypsin abolished the hCG-mediated inhibition of urokinase activity. The present findings offer an explanation for earlier observations that hCG reduced collagenase activity in trophoblasts without affecting the level of collagenase-specific mRNA. The present results are also consist with the concept that hCG, by its direct ability to inhibit certain serine proteases and urokinase in trophoblast, suppresses a protease-mediated conversion of procollagenase to active collagenase. The ability of hCG to prevent initiation of the collagenolytic cascade suggests that gonadotropins may regulate the transient invasive activity of the trophoblast.

L17 ANSWER 30 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

1990:890 Document No. 112:890 Differential regulation of cathepsin D by sex steroids in mammary cancer and uterine cells. Touitou, Isabelle; Cavailles, Vincent; Garcia, Marcel; Defrenne, Annick; Rochefort, Henri (Unite Horm. Cancer, INSERM, Montpellier, 34090, Fr.). Molecular and Cellular Endocrinology, 66(2), 231-8 (English) 1989. CODEN: MCEND6. ISSN: 0303-7207.

AB The precursor of cathepsin D, a lysosomal acidic ***protease*** , is secreted by ***human*** breast cancer cells, where its synthesis is specifically induced by estrogens and growth factors. The hormonal regulation of cathepsin D and its mRNA in uterine cells was investigated. In the Ishikawa endometrial cancer cell line, EGF increased the level of cathepsin D and its mRNA 2-3-fold. Although expression of the transiently-transfected estrogen-responsive recombinant (Vit.tk.CAT) and the endogenous progesterone receptor was markedly increased by estradiol in Ishikawa cells, estradiol did not alter the level of cathepsin D or its mRNA. The progestin R 5020 induced the expression of the LTR sp65 CAT, which contains the progesterone-responsive element of the MMTV, but it too was without effect on cathepsin D. By contrast, the expression of cathepsin D gene, in normal rat uterus, was increased by R 5020, but not by estradiol. Thus, cathepsin D gene expression is regulated differently by sex steroid hormones in endometrial and breast cancer cell lines, whereas it is similarly induced by EGF in these cells.

L17 ANSWER 31 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

1988:148071 Document No. 108:148071 Progesterone receptor structure and ***protease*** activity in primary ***human*** endometrial

carcinoma. Feil, Peter D.; Clarke, Christine L.; Satyaswaroop, Pondichery G. (Cancer Res. Cent., Pennsylvania State Univ., Hershey, PA, 17033, USA). Cancer Research, 48(5), 1143-7 (English) 1988. CODEN: CNREA8. ISSN: 0008-5472.

AB Monoclonal antibodies were used to investigate progesterone receptor structure (isoforms) in 33 primary human endometrial tumors. The monoclonal antibodies recognized on protein blots 2 progesterone receptor proteins with mol. wts. of 116,000 and 81,000. The 116,000-mol.-wt. protein appeared as a triplet, whereas a single band was found for the 81,000-mol.-wt. protein. The triplet/single structure was found in all progesterone receptor-pos. tumors, regardless of the degree of tumor differentiation. Protease activity, which gave rise to a false-neg. pattern on protein blots, was found in .apprx.50% of the tumors in which it was investigated. Inclusion of a cocktail of protease inhibitors during sample prepn. resulted in the maintenance of the triplet/singlet progesterone receptor structure. Mixing expts. using a progesterone receptor-rich human endometrial carcinoma (EnCa 101), which lacks protease activity, and protease-contg. primary tumor homogenates indicated that the protease was leupeptin sensitive. Interestingly, whereas the proteolytic activity reduced or eliminated the triplet/singlet progesterone receptor structure seen on protein blot anal., it did not affect progesterone receptor concn. measured by Scatchard anal. Sample prepn. in the presence of protease inhibitors is therefore a requisite for structural anal. of the progesterone receptor in endometrial tumors.

L17 ANSWER 32 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

1985:22223 Document No. 102:22223 DNA binding ability of estrogen receptors after interaction with cytosol from malignant human ***endometrium*** . Lenasi, H.; Hudnik-Plevnik, T.; Rainer, S.; Rakar, S. (Fac. Med., E. Kardelj Univ. Ljubljana, Ljubljana, Yugoslavia). Farmacevtski Vestnik (Ljubljana, Slovenia), 35(3), 227-32 (Slovenian) 1984. CODEN: FMVTAV. ISSN: 0014-8229.

AB Cytosols were prepd. from adenocarcinomas of human ***endometrium*** and from rat uterus. The influence of human tumor cytosol on the DNA binding ability of rat estrogen receptors was investigated. To eliminate the effect of the specific ***protease*** normally present in the ***human*** ***endometrium*** , which prevents the binding of estrogen receptors to DNA, all assays were performed in the presence of the inhibitor of serine protease, diisopropylfluorophosphate. The DNA binding ability to rat estrogen receptors was inhibited by all 12 specimens of human malignant endometrial cytosols. Since a conformational change of the receptor protein is believed to precede the binding of these mols. to DNA, the cytosols from adenocarcinomas of human ***endometrium*** probably contain an inhibitory factor which prevents either the activation of the receptors or interferes directly with the binding of receptors to DNA.

L17 ANSWER 33 OF 33 CAPLUS COPYRIGHT 2003 ACS on STN

1977:116584 Document No. 86:116584 Estrogen binding proteins of calf uterus. Molecular and functional characterization of the receptor transforming factor: a calcium ion-activated protease. Puca, Giovanni Alfredo; Nola, Ernesto; Sica, Vincenzo; Bresciani, Francesco (Fac. Med. Chir. I, Univ. Napoli, Naples, Italy). Journal of Biological Chemistry, 252(4), 1358-66 (English) 1977. CODEN: JBCHA3. ISSN: 0021-9258.

AB Calf uterus cytosol contains a Ca2+-activated receptor transforming factor (RTF) which irreversibly converts the larger mol. states of estrogen receptor into a smaller, salt-stable form. A method is described for sepn. of precursor and RTF-transformed receptor forms, which takes advantage of a difference in isoelec. point between the 2; the more acidic precursor is still retained by DEAE-cellulose under conditions which produce release from cellulose of the less acidic transformed form. Based on this method of sepn., RTF activity can be assayed easily. The purifn. and phys. and functional characterization of this RTF is now possible. It was purified .apprx.100-fold and its mol. properties detd. RTF attacks native casein but not Hb, ovalbumin, or albumin. N-Benzoylarginine Me ester is a competitive inhibitor of RTF-induced receptor transformation, whereas L-leucylglycylglycine and N-benzoyltyrosinamide are not. RTF activity is protected by SH compds. and is Ca2+-dependent. Ca2+ starts an activation-inactivation cycle of RTF, with permanent loss of transforming activity which proceeds at a particularly fast rate in the absence of substrate. Mg2+ is inactive, while Sr2+ and Mn2+ may in part substitute

for Ca2+. RTF is present in both ***endometrium*** and myometrium. It is not a lysosomal hydrolase, as shown by its alk. pH optimum and exclusive location in cytosol, nor is it trypsin or a protease of the trypsin group. Also, it is distinct from known ***proteases*** of ***human*** uterus. The functional significance of this Ca2+-activated protease of cytosol with alk. pH optimum and high affinity for the larger native form of receptor is still unknown.

=> S LUNG
147762 LUNG
38775 LUNGS
L18 161095 LUNG
(LUNG OR LUNGS)

=> S L5 AND L18
L19 282 L5 AND L18

=> S L5 (4A) L18
L20 56 L5 (4A) L18

=> S L20 NOT (L7,L9,L11,L14,L17)
L21 54 L20 NOT ((L7 OR L9 OR L11 OR L14 OR L17))

=> D 1-54 CBIB ABS

L21 ANSWER 1 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2003:417867 Document No. 139:2880 Nucleic acids encoding human serine protease 17 and their use as tumor markers and in diagnostics and therapeutics. Madison, Edwin L.; Ong, Edgar O. (Corvas International, Inc., USA). PCT Int. Appl. WO 2003044179 A2 20030530, 189 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US37626 20021120. PRIORITY: US 2001-PV332015 20011120.
AB Provided herein are serine proteinase polypeptides designated CVSP17 that exhibit protease activity as a single chain or as an activated two chain form. In particular, the invention provides the protease domain of CVSP17 (residues 105-332), where activation cleavage of CVSP17 is between the Arg-104 and Ile-105, or a variant where there is an Arg at position 258 in place of a Glu. CVSP17 is a member of the serine protease family whose functional activity differs in tumor cells from nontumor cells in the same tissue. CVSP17 is expressed as a secreted protein and may also bind to the cell surface receptors and function as a cell-surface bound protease, such as by dimerization or multimerization with a membrane-bound or receptor-bound protein. Sequence anal. indicates the presence of a sequence of amino acids at the C-terminus that is consonant with a leucine zipper, which facilitates dimerization, and hence it may have a regulatory function as well. CVSP17 is expressed or activated in cervical tumors, colon carcinoma, and pancreas islet cell tumors, and may also be expressed and/or activated in other tumors and can serve as a tumor marker. Methods using the polypeptides to identify compds. that modulate the protease activity thereof are provided.

L21 ANSWER 2 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2003:18208 Document No. 138:382598 Cysteine protease activity is required for surfactant protein B processing and lamellar body genesis. Guttentag, Susan; Robinson, Lauren; Zhang, Peggy; Brasch, Frank; Buhling, Frank; Beers, Michael (Division of Neonatology, Department of Pediatrics, University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, 19104-4318, USA). American Journal of Respiratory Cell and Molecular Biology, 28(1), 69-79 (English) 2003. CODEN: AJRBEL. ISSN: 1044-1549. Publisher: American Thoracic Society.
AB Surfactant protein (SP)-B is essential for lamellar body genesis and for the final steps in proSP-C post-translational processing. The mature SP-B

protein is derived from multistep processing of the primary translation product proSP-B; however, the enzymes required for these events are currently unknown. Recent ultra-structural colocalization studies have suggested that the cysteine protease Cathepsin H may be involved in proSP-B processing. Using models of isolated human type 2 cells in culture, we describe the effects of cysteine protease inhibition by E-64 on SP-B processing and type 2 cell differentiation. Pulse-chase labeling and Western immunoblotting studies showed that the final step of SP-B processing, specifically cleavage of SP-B9 to SP-B8, was significantly inhibited by E-64, resulting in delayed accumulation of SP-B8 without adverse effects on SP-A or glyceraldehyde phosphate dehydrogenase expression. E-64 treatment during type 2 cell differentiation mimicked features of inherited SP-B deficiency in humans and mice, specifically disrupted lamellar body genesis, and aberrant processing of proSP-C. Reverse transcriptase-polymerase chain reaction and Western immunoblotting studies showed that cathepsin H is induced during in vitro differentiation of type 2 cells and localizes with SP-B in multivesicular bodies, composite bodies, and lamellar bodies by immunoelectron microscopy. Furthermore, cathepsin H activity was specifically inhibited in a dose-dependent fashion by E-64. Our data show that a cysteine protease is involved in SP-B processing, lamellar body genesis, and SP-C processing, and suggest that Cathepsin H is the most likely candidate protease.

L21 ANSWER 3 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN

2002:754612 Document No. 137:275019 Human transmembrane serine protease MTSP9 and cDNA and methods for drug screening and for cancer diagnosis and treatment. Madison, Edwin L.; Ong, Edgar O. (Corvas International, Inc., USA). PCT Int. Appl. WO 2002077267 A2 20021003, 199 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US9611 20020327. PRIORITY: US 2001-PV279228 20010327; US 2001-PV291501 20010515.

AB Provided herein are human type II transmembrane serine protease 9 (MTSP9) and cDNA encoding it. Anti-MTSP9 antibodies and MTSP9 gene-inhibiting dsRNA and antisense nucleic acids may be used to treat cancers. Probes for MTSP9 nucleic acids may be used to diagnose cancer or predisposition to cancer. The MTSP9 protein may be used in screening for inhibitors of the zymogen form or inhibitors of the two-chain form. Thus, the cDNA for the 418-amino acid MTSP9 was cloned and sequenced. The protein exhibited 42% sequence identity with human endotheliase 1 and 40% with another type II membrane-type serine proteinase, human airway trypsin-like serine proteinase. The MTSP9 gene was highly expressed in the esophagus and a low levels in many other tissues. The gene was also expressed in esophageal tumors and in lung carcinoma.

L21 ANSWER 4 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN

2002:716447 Document No. 137:243919 Human transmembrane serine protease MTSP7 and cDNA and their uses in cancer diagnosis and treatment and drug screening. Madison, Edwin L.; Ong, Edgar O. (Corvas International, Inc., USA). PCT Int. Appl. WO 2002072786 A2 20020919, 184 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US7903 20020313. PRIORITY: US 2001-PV275592 20010313.

AB Provided herein is a human type II transmembrane serine protease 7 (MT-SP7) and cDNA encoding it. Zymogen and activated forms of MTSP7 as well as single and two chain forms of the protease domain are also provided. Methods using the proteins to identify compds. that modulate the protease activity of an MTSP7 are provided. Thus, the cDNA for human MTSP7 was cloned, sequenced, and the protease domain-encoding DNA

expressed in Pichia pastoris. The MTSP7 gene was ubiquitously expressed in human tissues and was also highly expressed in lung carcinoma, leukemia, and cervical carcinoma cell lines. The protein sequence exhibited 42% sequence identity with human endotheliase 1. MTSP7 has a transmembrane domain at the N-terminus followed by a SEA domain. The C-terminal portion comprises the protease domain.

L21 ANSWER 5 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2002:290986 Document No. 136:305174 Human signal peptidase sequence homolog 10 and its cDNA and therapeutic use thereof. Mao, Yumin; Xie, Yi (Bode Gene Development Co., Ltd., Shanghai, Peop. Rep. China). Faming Zhuanli Shenqing Gongkai Shuomingshu CN 1315564 A 20011003, 32 pp. (Chinese). CODEN: CNXXEV. APPLICATION: CN 2000-115215 20000328.
AB The invention provides cDNA sequences of a novel human signal peptidase sequence homolog 10 (named by protein MW detected in SDS-PAGE gel) cloned from human embryonic brain. The invention also relates to constructing the cloned gene expression vectors to prep. its recombinant protein using E. coli cells or eukaryotic cells. Methods of expressing and prepg. the above recombinant protein and its antibody are described. The mRNA expression profile in various normal or tumor cell lines and tissues is also provided. Methods of using related gene or protein products for the treatment of signal peptidase 10-related diseases (such as malignant tumor, blood disease, HIV infection, immune disease, or inflammation). Methods for screening for related analogs, agonists, inhibitors and antagonists to be used as therapeutic drugs are also described.

L21 ANSWER 6 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2001:935759 Document No. 136:65251 Human prostasin-like serine protease and cDNA and their use in drug screening and disease diagnosis and treatment. Xiao, Yonghong; Morozov, Vladimir (Bayer Aktiengesellschaft, Germany). PCT Int. Appl. WO 2001098467 A2 20011227, 111 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP7117 20010622. PRIORITY: US 2000-PV213588 20000623; US 2001-PV276909 20010320.
AB Human prostasin-like serine protease and cDNA are disclosed. Its mRNA expression profile in various human tissues, neutrophil-like cell lines, and cancer cells is provided. Recombinant cells expressing this cDNA can be used to prep. the enzyme. These recombinant cells, the enzyme, or nucleic acids encoding the enzyme are useful in screening for modulators of the enzymic activity or gene expression. Methods of screening for its modulators and using them for the treatment of various disease models and testing their effectiveness are described. Reagents which regulate human prostasin-like serine protease activity and reagents which bind to human prostasin-like serine protease gene products can be used to regulate extracellular matrix degrdn. Such regulation is particularly useful for treating chronic obstructive pulmonary disease, metastasis of malignant cells, tumor, angiogenesis, inflammation, atherosclerosis, neurodegenerative diseases, and pathogenic infections.

L21 ANSWER 7 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2001:935758 Document No. 136:65250 Human prostasin-like serine protease and cDNA and their use in drug screening and disease diagnosis and treatment. Xiao, Yonghong (Bayer Aktiengesellschaft, Germany). PCT Int. Appl. WO 2001098466 A2 20011227, 125 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP7116 20010622. PRIORITY: US 2000-PV213474 20000623; US 2001-PV277612 20010322.
AB Human prostasin-like serine protease and cDNA are disclosed. Its mRNA expression profile in various human tissues, neutrophil-like cell lines,

and cancer cells is provided. Recombinant cells expressing this cDNA can be used to prep. the enzyme. These recombinant cells, the enzyme, or nucleic acids encoding the enzyme are useful in screening for modulators of the enzymic activity or gene expression. Methods of screening for its modulators and using them for the treatment of various disease models and testing their effectiveness are described. Reagents which regulate human prostasin-like serine protease activity and reagents which bind to human prostasin-like serine protease gene products can be used to regulate extracellular matrix degrdn. Such regulation is particularly useful for treating chronic obstructive pulmonary disease, metastasis of malignant cells, tumor, angiogenesis, inflammation, atherosclerosis, neurodegenerative diseases, and pathogenic infections.

L21 ANSWER 8 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2001:923980 Document No. 136:49409 Human transmembrane serine protease and cDNA and their use in drug screening and disease diagnosis and treatment. Xiao, Yonghong; Gedrich, Richard (Bayer Aktiengesellschaft, Germany). PCT Int. Appl. WO 2001096538 A2 20011220, 120 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP6618 20010612. PRIORITY: US 2000-PV211224 20000613; US 2001-PV283353 20010413; US 2001-PV283648 20010416.

AB Human transmembrane serine protease and cDNA are disclosed. Its mRNA expression profile in various human tissues, neutrophil-like cell lines, and cancer cells is provided. Recombinant cells expressing this cDNA can be used to prep. the enzyme. These recombinant cells, the enzyme, or nucleic acids encoding the enzyme are useful in screening for modulators of the enzymic activity or gene expression. Methods of screening for its modulators and using them for the treatment of various disease models and testing their effectiveness are described. Reagents which regulate human transmembrane serine protease activity and reagents which bind to human transmembrane serine protease gene products can be used to regulate extracellular matrix degrdn. Such regulation is particularly useful for treating chronic obstructive pulmonary disease, metastasis of malignant cells, tumor, angiogenesis, inflammation, atherosclerosis, neurodegenerative diseases, and pathogenic infections.

L21 ANSWER 9 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2001:890305 Document No. 136:214635 In situ detection of the mast cell ***proteases*** chymase and tryptase in ***human*** ***lung*** tissue using light and electron microscopy. Beil, Waltraud J.; Pammer, Johannes (Department of Clinical Pathology, Allgemeines Krankenhaus, Vienna, 1090, Austria). Histochemistry and Cell Biology, 116(6), 483-493 (English) 2001. CODEN: HCBIFP. ISSN: 0948-6143. Publisher: Springer-Verlag.

AB Scroll-rich, 'mucosal' mast cells are the predominant human lung mast cell type. It has been proposed that these mast cells store tryptase but are mostly chymase deficient. We present a detailed immunolocalization study of chymase and tryptase in lung specimens of eight patients. Using monoclonal antibody B7 in a conventional tissue processing method for light microscopy, chymase-pos. mast cells were much fewer than tryptase-pos. ones. However, they approached the no. of tryptase-pos. cells when optimized processing was used. Two different monoclonal antibodies, B7 and CC1, were used to visualize chymase in purified lung mast cells of two patients using ultrastructural immunogold labeling. Immunoabsorption controls demonstrated a reactivity of B7 with both tryptase and chymase, but indicated specificity of CC1 for chymase. On the ultrastructural level, all of more than 1,400 lung mast cells evaluated labeled for chymase. Reactivity was seen in cytoplasmic granules, cytoplasm and vesicles, but not elsewhere. Tryptase labeling using monoclonal antibody G3 was also present in all mast cells detected, and was retained in altered granules (=activated mast cells), where B7 labeling was sparse. The av. labeling d. was approx. sixfold higher than for chymase. In summary, chymase may be more abundant in human lung mast cells than hitherto thought.

L21 ANSWER 10 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2001:842890 Document No. 136:338356 Importance of lysosomal cysteine proteases in lung disease. Wolters, Paul J.; Chapman, Harold A. (Department of Medicine and Cardiovascular Research Institute, University of California, San Francisco, CA, USA). Respiratory Research [online computer file], 1(3), 170-177 (English) 2000. CODEN: RREEBZ. ISSN: 1465-993X. URL: http://respiratory-research.com/content/1/3/170 Publisher: BioMed Central Ltd..
AB A review. The human lysosomal cysteine proteases are a family of 11 proteases whose members include cathepsins B, C, H, L, and S. The biol. of these proteases was largely ignored for decades because of their lysosomal location and the belief that their function was limited to the terminal degrdn. of proteins. In the past 10 yr, this view has changed as these proteases have been found to have specific functions within cells. This review highlights some of these functions, specifically their roles in matrix remodeling and in regulating the immune response, and their relationship to lung diseases.

L21 ANSWER 11 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2001:816939 Document No. 135:353886 Human protease sequence homologs, protein and cDNA sequences, chromosomal mapping and single nucleotide polymorphism. Plowman, Gregory D.; Whyte, David; Sudarsanam, Sucha; Manning, Gerard; Caenepeel, Sean; Payne, Vilia (Sugen, Inc., USA). PCT Int. Appl. WO 2001083782 A2 20011108, 232 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US14431 20010504. PRIORITY: US 2000-PV201879 20000504.
AB 35 Human protease sequence homolog, including aspartic proteinase, cysteine proteinase and metallo-proteinase sequence homolog, were identified through bioinformatics search. The invention also relates to chromosomal location of genes for protease sequence homolog and single nucleotide polymorphism found in said genes. The invention also relates to identify modulators of protease sequence homolog and use in therapy. The invention also relates to recombinant expression of said protease sequence homolog. and uses of said protease sequence homolog in diagnosis.

L21 ANSWER 12 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2001:735504 Document No. 136:260785 A novel serine protease SNC19 associated with human colorectal cancer. Cao, Jiang; Zheng, Shu; Zheng, Lei; Cai, Xinhan; Zhang, Yanming; Geng, Liyi; Fang, Yongming (Cancer Institute, Zhejiang University, Hangzhou, 310009, Peop. Rep. China). Chinese Medical Journal (Beijing, China, English Edition), 114(7), 726-730 (English) 2001. CODEN: CMJODS. ISSN: 0366-6999. Publisher: Chinese Medical Association.
AB Objective: To study the structure and function of a novel serine protease gene assocd. with human colorectal cancer SNC19. Methods: The cDNA sequence was detd. by both manual and automatic sequencing techniques. The full length cDNA sequence was obtained by the 5'-Rapid Amplification of cDNA Ends technique and web-based anal. Open reading frame anal. and protein function prediction were also performed. Northern blot was used to detect the expression of SNC19 in various human normal tissues and tumor cell lines. Fluorescent in situ hybridization combined with fluorescent R-banding technique was employed to map the SNC19 gene on human chromosome. Results: Full length SNC19 cDNA, size 3152 bp, encodes a protein highly homologous to a mouse serine protease epithin. In normal human tissues, high SNC19 expression levels were obsd. in the kidney, pancreas, prostate, small intestine and colon; moderate SNC19 expression levels were obsd. in the placenta, lung, liver, spleen, thymus, testis and peripheral blood lymphocytes; and extremely low expression levels were obsd. in the heart, brain, skeletal muscle and ovary. In tumor cell lines, colorectal cancer cells SW480, SW620, SW1116 and Colo205, breast cancer cell Bcap37 and gastric cancer cells MKN28 and SGC7901 showed high levels of SNC19 expression; cervical cancer cell HeLa-S3, lung cancer PAA, oral epithelial cancer cell KB and lymphoma cell Raji showed moderate levels of SNC19 expression; and tongue squamous cancer cell Tca8113,

leukemia cells HL-60, K562, MOLT-4, lung cancer cell A549 and melanoma cell G361 showed very low levels of SNC19 expression. SNC19 was mapped to human chromosome 11q24-25. Conclusion: SNC19 encodes a novel human serine protease with 855 amino acid residues. As a novel serine protease assocd. with human colorectal cancer, the expression of SNC19 in various tissues and cell lines may have very important impact on their phenotypes and biol. behaviors.

L21 ANSWER 13 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2001:219059 Document No. 135:178967 Distribution of tripeptidyl peptidase I in human tissues under normal and pathological conditions. Kida, Elizabeth; Golabek, Adam A.; Walus, Mariusz; Wujek, Peter; Kaczmarski, Wojciech; Wisniewski, Krystyna E. (Department of Pathological Neurobiology, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, 10314, USA). Journal of Neuropathology and Experimental Neurology, 60(3), 280-292 (English) 2001. CODEN: JNENAD. ISSN: 0022-3069. Publisher: American Association of Neuropathologists, Inc..

AB Tripeptidyl peptidase I (TPP I) is a lysosomal exopeptidase that cleaves tripeptides from the free N-termini of oligopeptides. Mutations in this enzyme are assocd. with the classic late-infantile form of neuronal ceroid lipofuscinosis (CLN2), an autosomal recessive disorder leading to severe brain damage. To gain more insight into CLN2 pathogenesis and the role of TPP I in human tissues in general, the authors analyzed the temporal and spatial distribution of TPP I in the brain and its localization in internal organs under normal and pathol. conditions. The authors report that TPP I immunoreactivity appears in neurons late in gestation and increases gradually in the postnatal period, matching significantly the final differentiation and maturation of neural tissue. Endothelial cells, choroid plexus, microglial cells, and ependyma showed TPP I immunostaining distinctly earlier than neurons. Acquisition of the adult pattern of TPP I distribution in the brain at around the age of 2 yr correlates with the onset of clin. signs in CLN2 subjects. In adults, TPP I was found in all types of cells in the brain and internal organs the authors studied, although the intensity of TPP I labeling varied among several types of cells and showed a noticeable predilection for cells and/or organs assocd. with peptide hormone and neuropeptide prodn. In addn., TPP I immunoreactivity was increased in aging brain, neurodegenerative and lysosomal storage disorders, and some differentiated neoplasms and was reduced in ischemic/anoxic areas and undifferentiated tumors. These findings suggest that TPP I is involved in general protein turnover and that its expression may be controlled by various regulatory mechanisms, which highlights the importance of this enzyme for normal function of cells and organs in humans.

L21 ANSWER 14 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2000:654261 Document No. 133:234461 Human serine protease, Trypsin hL, cDNA, and recombinant expression. Imamura, Yasuhiro; Ariga, Hiroyoshi; Kido, Hiroshi (Mistubishi Tokyo Pharmaceuticals Inc., Japan). Jpn. Kokai Tokkyo Koho JP 2000253887 A2 20000919, 17 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1999-65337 19990311.

AB A novel human serine protease, Trypsin hL, cDNA, and recombinant expression, are disclosed. Recombinant human Trypsin hL expressed in E. coli showed protease activity toward Boc-Phe-Ser-Arg-MCA. Specific expression in human lung was obsd.

L21 ANSWER 15 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2000:628170 Document No. 133:219455 Human transmembrane serine protease TADG-12 overexpressed in ovarian carcinoma and diagnosis and treatment of cancer. O'Brien, Timothy J.; Underwood, Lowell J. (The Board of Trustees of the University of Arkansas, USA). PCT Int. Appl. WO 2000052044 A1 20000908, 118 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US5612 20000302. PRIORITY: US 1999-261416 19990303.

AB The present invention provides TADG-12 (Tumor-Assocd. Differentially expressed Gene 12) proteins and cDNAs encoding such proteins. Also provided is a vector/host cell capable of expressing the DNA. The present invention further provides various methods of early detection of assocd. ovarian and other malignancies, and of interactive therapies for cancer treatment by utilizing the DNA and/or protein disclosed herein. Thus, to

examine the serine proteases expressed by ovarian cancers, a PCR-based differential display technique was employed utilizing redundant PCR primers corresponding to the most highly conserved amino acids in these enzymes. A novel cell-surface, multidomain serine proteinase (TADG-12) was identified. The extracellular nature of TADG-12 may allow tumor detection via a TADG-12-specific assay. Addnl., a splicing variant of TADG-12 was detected at elevated levels in 35% of the tumors that were examd. This variant is a truncated form of TADG-12 with an altered amino acid sequence which may be a unique tumor-specific target for therapeutic approaches.

L21 ANSWER 16 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
2000:125191 Document No. 132:263395 Mast cell tryptase stimulates ***human*** ***lung*** fibroblast proliferation via ***protease*** -activated receptor-2. Akers, Ian A.; Parsons, Maddy; Hill, Michael R.; Hollenberg, Morley D.; Sanjar, Shahin; Laurent, Geoffrey J.; McAnulty, Robin J. (Centre for Cardiopulmonary Biochemistry and Respiratory Medicine, The Rayne Institute, The Royal Free and University College Medical School, London, WC1E 6JJ, UK). American Journal of Physiology, 278(1, Pt. 1), L193-L201 (English) 2000. CODEN: AJPHAP. ISSN: 0002-9513. Publisher: American Physiological Society.

AB Mast cells play a potentially important role in fibroproliferative diseases, releasing mediators including tryptase that are capable of stimulating fibroblast proliferation and procollagen synthesis. The mechanism by which tryptase stimulates fibroblast proliferation is unclear, although recent studies suggest it can activate protease-activated receptor (PAR)-2. We therefore investigated the role of PAR-2 in tryptase-induced proliferation of human fetal lung and adult lung parenchymal and airway fibroblasts and, for comparative purposes, adult dermal fibroblasts. Tryptase (0.7-70 mU/mL) induced concn.-dependent increases in proliferation of all fibroblasts studied. Antipain, bis(5-amidino-2-benzimidazolyl)methane, and benzamidine inhibited tryptase-induced fibroblast proliferation, demonstrating that proteolytic activity is required for the proliferative effects of tryptase. RT-PCR demonstrated the presence of PAR-2 mRNA, and immunohistochem. staining localized PAR-2 to the cell surface of lung fibroblasts. In addn., specific PAR-2 activating peptides, SLIGKV and SLIGRL, mimicked the proliferative effects of tryptase. In contrast, human dermal fibroblasts only weakly stained with the PAR-2 antibody, PAR-2 mRNA was almost undetectable, and fibroblasts did not respond to PAR-2 activating peptides. These results suggest that tryptase induces lung, but not dermal, fibroblast proliferation via activation of PAR-2 and are consistent with the hypothesis that the release of tryptase from activated mast cells may play an important role in the fibroproliferative response obsd. in asthma, chronic obstructive pulmonary disease, and patients with pulmonary fibrosis.

L21 ANSWER 17 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1999:816597 Document No. 132:206448 Membrane-anchored aspartyl protease with Alzheimer's disease .beta.-secretase activity. Yan, Riqiang; Bienkowski, Michael J.; Shuck, Mary E.; Miao, Huiyi; Tory, Monica C.; Pauley, Adele M.; Brashler, John R.; Stratman, Nancy C.; Mathews, W. Rodney; Buhl, Allen E.; Carter, Donald B.; Tomasselli, Alfredo G.; Parodi, Luis A.; Heinrikson, Robert L.; Gurney, Mark E. (Cell & Molecular Biology, Genomics, Protein Sciences, Pharmacology, Structural, Analytical & Medicinal Chemistry and Neurobiology, Pharmacia & Upjohn, Inc., Kalamazoo, MI, 49007, USA). Nature (London), 402(6761), 533-537 (English) 1999. CODEN: NATUAS. ISSN: 0028-0836. Publisher: Macmillan Magazines.

AB Mutations in the gene encoding the amyloid protein precursor (APP) cause autosomal dominant Alzheimer's disease. Cleavage of APP by unidentified proteases, referred to as .beta.- and .gamma.-secretases, generates the amyloid .beta.-peptide, the main component of the amyloid plaques found in Alzheimer's disease patients. The disease-causing mutations flank the protease cleavage sites in APP and facilitate its cleavage. Here the authors identify a new membrane-bound aspartyl protease (Asp2) with .beta.-secretase activity. The Asp2 gene is expressed widely in brain and other tissues. Decreasing the expression of Asp2 in cells reduces amyloid .beta.-peptide prodn. and blocks the accumulation of the carboxy-terminal APP fragment that is created by .beta.-secretase cleavage. Solubilized Asp2 protein cleaves a synthetic APP peptide substrate at the .beta.-secretase site, and the rate of cleavage is increased tenfold by a

mutation assocd. with early-onset Alzheimer's disease in Sweden. Thus, Asp2 is a new protein target for drugs that are designed to block the prodn. of amyloid .beta.-peptide peptide and the consequent formation of amyloid plaque in Alzheimer's disease.

L21 ANSWER 18 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1999:711150 Document No. 132:34201 .beta.-Secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Vassar, Robert; Bennett, Brian D.; Babu-Khan, Safura; Kahn, Steve; Mendiaz, Elizabeth A.; Denis, Paul; Teplow, David B.; Ross, Sandra; Amarante, Patricia; Loeloff, Richard; Luo, Yi; Fisher, Seth; Fuller, Janis; Edenson, Steven; Lile, Jackson; Jarosinski, Mark A.; Biere, Anja Leona; Curran, Eileen; Burgess, Teresa; Louis, Jean-Claude; Collins, Frank; Treanor, James; Rogers, Gary; Citron, Martin (Amgen, Inc, Thousand Oaks, CA, 91320-1799, USA). Science (Washington, D. C.), 286(5440), 735-741 (English) 1999. CODEN: SCIEAS. ISSN: 0036-8075. Publisher: American Association for the Advancement of Science.
AB Cerebral deposition of amyloid .beta. peptide (A.beta.) is an early and crit. feature of Alzheimer's disease. A.beta. generation depends on proteolytic cleavage of the amyloid precursor protein (APP) by two unknown proteases: .beta.-secretase and .gamma.-secretase. These proteases are prime therapeutic targets. A transmembrane aspartic protease with all the known characteristics of .beta.-secretase was cloned and characterized. Overexpression of this protease, termed BACE (for beta-site APP-cleaving enzyme) increased the amt. of .beta.-secretase cleavage products, and these were cleaved exactly and only at known .beta.-secretase positions. Antisense inhibition of endogenous BACE mRNA decreased the amt. of .beta.-secretase cleavage products, and purified BACE protein cleaved APP-derived substrates with the same sequence specificity as .beta.-secretase. Finally, the expression pattern and subcellular localization of BACE were consistent with that expected for .beta.-secretase. Future development of BACE inhibitors may prove beneficial for the treatment of Alzheimer's disease.

L21 ANSWER 19 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1999:640986 Document No. 131:283053 Human protease-activated receptor PAR4 and its cDNA and pharmaceuticals containing the PAR4 ligand. Xu, Wen-feng; Presnell, Scott R.; Yee, David P.; Foster, Donald C. (Zymogenetics, Inc., USA; University of Washington). PCT Int. Appl. WO 9950415 A2 19991007, 85 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US7100 19990331. PRIORITY: US 1998-53866 19980401.
AB The present invention relates to PAR4, a novel member of the protease-activated receptor family, and DNA encoding it. PAR4 mediates biol. responses and/or cellular signaling in response to proteases. Protease cleavage of PAR4 exposes a PAR4 extracellular amino terminal portion that serves as a ligand for the PAR4 receptor. PAR4 may be used as a target in drug screening, and further used to identify proteinaceous or non-proteinaceous PAR4 agonists and antagonists. The present invention also includes antibodies to the PAR4 polypeptides. A partial cDNA sequence for PAR4 was identified in an expressed sequence tag database, and the full-length cDNA clone was then isolated from a lymphoma Daudi cell cDNA library. The ORF codes for a seven transmembrane domain protein of 385 amino acids with 33% amino acid sequence identity with PAR1, PAR2, and PAR3. A putative protease cleavage site (Arg-47/Gly-48) was identified within the extracellular amino terminus. COS cells transiently transfected with PAR4 resulted in the formation of intracellular inositol triphosphate when treated with either thrombin or trypsin. A PAR4 mutant in which Arg-47 was replaced with Ala did not respond to thrombin or trypsin. A hexapeptide (GYPGQV) representing the newly exposed tethered ligand from the amino terminus of PAR4 after proteolysis by thrombin activated COS cells transfected with either wild-type or the mutant PAR4. Northern blot showed that PAR4 mRNA was expressed in a no. of human tissues, with high levels being present in lung, pancreas, thyroid, testis, and small intestine. By fluorescence in situ hybridization, the

human PAR4 gene was mapped to chromosome 19p12.

L21 ANSWER 20 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1999:273001 Document No. 131:100193 Peptidases: structure, function and modulation of peptide-mediated effects in the human lung. Van Der Velden, V. H. J.; Hulsmann, A. R. (Department of Immunology, Erasmus University, Rotterdam, 3000 DR, Neth.). Clinical and Experimental Allergy, 29(4), 445-456 (English) 1999. CODEN: CLEAEN. ISSN: 0954-7894. Publisher: Blackwell Science Ltd..
AB A review with 50 refs. describing (1) biochem. and mol. characteristics, gene structure, tissue distribution, enzymic activity, and biol. functions of neutral endopeptidase, aminopeptidase N, dipeptidyl peptidase IV, and other peptidases, and (2) modulation of peptide-mediated inflammation in lung.

L21 ANSWER 21 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1999:25793 Document No. 130:235622 Cysteine proteases and cysteine protease inhibitors in non-small cell lung cancer. Krepela, E.; Prochazka, J.; Karova, B.; Cermak, J.; Roubkova, H. (Department of Molecular and Cellular Pneumology, Clinic of Pneumology and, Medical Faculty Hospital Bulovka, Prague, 180 71, Czech Rep.). Neoplasma, 45(5), 318-331 (English) 1998. CODEN: NEOLA4. ISSN: 0028-2685. Publisher: Slovak Academic Press Ltd..
AB In this study we investigated the levels of two lysosomal cysteine protease proteins cathepsin B (CB) and cathepsin L (CL) and the levels of three cysteine protease inhibitor proteins stefin A (SFA), stefin B (SFB) and cystatin C (CNC) in squamous-cell lung carcinoma (SQCLC) and matched lung parenchyma specimens and examd. the inhibition of CB and cathepsin C (CC) activities by endogenous inhibitors in exts. from SQCLC, lung adenocarcinoma (LAC) and lung parenchyma specimens. We found that Stage I SQCLCs contained significantly increased levels of CB protein, CB activity and SFA protein as compared to matched lungs. Neither the levels of CL protein nor the levels of SFB protein nor the levels of CNC protein in Stage I SQCLCs and the lungs were significantly different, but the levels of CB and CL proteins as well as the levels of SFA and SFB proteins showed significant pos. correlation in SQCLCs. In SQCLCs as well as in the lungs the level of SFB protein was significantly higher than the level of SFA protein or the level of CNC protein. In the lungs the levels of SFA protein and CNC protein revealed a weak neg. correlation trend. In exts. from SQCLCs the level of SFA protein showed a weak neg. correlation with the residual CB activity (i.e. the activity remaining after ext. preincubation) whereas in exts. from the lungs the level of CNC protein displayed a weak neg. correlation trend with the residual CB activity and with the residual CC activity. We obsd. that SQCLCs and LACs contained not only a significantly increased activity of CB but also a significantly higher inhibitory potential against the activity of endogenous CB as compared to matched lungs. Leupeptin, a small inhibitor of CB, protected CB in lung carcinoma and lung parenchyma exts. from preincubation-induced inhibition, revealing an active-site directed and competitive nature of CB inhibition by endogenous cystatins. Ultrafiltration passaged protein prepns. of nominal Mr .ltoreq. 30 000 obtained from exts. of SQCLCs inhibited significantly higher quantities of activity of purified bovine spleen CC than did such protein prepns. from matched lungs. Reaction courses of purified bovine spleen CC that had been preincubated with such protein prepns. resembled those of endogenous CC from SQCLC and lung exts. showing a slow steady-state approach. These observations and the relaxation kinetics of CC from SQCLC and lung exts. suggest that CC in the exts. may be complexed with some cystatins. In conclusion, our results indicate that quant. different combinations of cystatins are the major constituents of the inhibitory potential against CB and CC in SQCLCs and the lungs.

L21 ANSWER 22 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1998:728578 Document No. 130:1191 human and mouse neurotrypsin sequence and therapeutic applications. Sonderegger, Peter (Switz.). PCT Int. Appl. WO 9849322 A1 19981105, 51 pp. DESIGNATED STATES: W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-IB625 19980424. PRIORITY: CH 1997-966 19970426.

AB Neurotrypsin is a newly discovered serine protease which is predominantly expressed in the brain and lungs. There are described neurotrypsins of the formulas (I) or (II), including the sep. coding and coded sequences of these compds. of the formulas (I) or (II). These compds. may be used as at least one active compd. in a pharmaceutical component. The coded peptide sequences of these compds. may be used as targets for the development of pharmaceutical drugs.

L21 ANSWER 23 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1998:378455 Document No. 129:131335 Cloning and characterization of human protease-activated receptor 4. Xu, Wen-Feng; Andersen, Henrik; Whitmore, Theodore E.; Presnell, Scott R.; Yee, David P.; Ching, Andrew; Gilbert, Teresa; Davie, Earl W.; Foster, Donald C. (Department of Biochemistry, University of Washington, Seattle, WA, 98195-7350, USA). Proceedings of the National Academy of Sciences of the United States of America, 95(12), 6642-6646 (English) 1998. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.
AB Protease-activated receptors 1-3 (PAR1, PAR2, and PAR3) are members of a unique G protein-coupled receptor family. They are characterized by a tethered peptide ligand at the extracellular amino terminus that is generated by minor proteolysis. A partial cDNA sequence of a fourth member of this family (PAR4) was identified in an expressed sequence tag database, and the full-length cDNA clone has been isolated from a lymphoma Daudi cell cDNA library. The ORF codes for a seven transmembrane domain protein of 385 amino acids with 33% amino acid sequence identity with PAR1, PAR2, and PAR3. A putative protease cleavage site (Arg-47/Gly-48) was identified within the extracellular amino terminus. COS cells transiently transfected with PAR4 resulted in the formation of intracellular inositol triphosphate when treated with either thrombin or trypsin. A PAR4 mutant in which the Arg-47 was replaced with Ala did not respond to thrombin or trypsin. A hexapeptide (GYPGQV) representing the newly exposed tethered ligand from the amino terminus of PAR4 after proteolysis by thrombin activated COS cells transfected with either wild-type or the mutant PAR4. Northern blot showed that PAR4 mRNA was expressed in a no. of human tissues, with high levels being present in lung, pancreas, thyroid, testis, and small intestine. By fluorescence in situ hybridization, the human PAR4 gene was mapped to chromosome 19p12.

L21 ANSWER 24 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1998:252722 Document No. 129:106960 Identification of a novel serine protease-like molecule in human brain. Meckelein, Barbara; Marshall, Derek C. L.; Conn, Kelly-Jo; Pietropaolo, Michael; Van Nostrand, William; Abraham, Carmela R. (The Arthritis Center, Departments of Biochemistry, Boston University School of Medicine, Boston, MA, 02118-2394, USA). Molecular Brain Research, 55(2), 181-197 (English) 1998. CODEN: MBREE4. ISSN: 0169-328X. Publisher: Elsevier Science B.V..
AB Proteolysis of the amyloid .beta. protein precursor (APP) is a key event in the development of Alzheimer's disease. In the authors' search for proteases that can cleave APP and liberate the N-terminus of the amyloidogenic .beta. protein, the authors characterized a calcium-dependent serine protease (CASP) which is present in reactive astrocytes and cross-reacts with anti-cathepsin G antibodies. The authors wanted to take advantage of this cross-reactivity to clone the cDNA of CASP and eventually evaluate its tissue distribution. Screening of two human fetal brain cDNA libraries with anti-cathepsin G antibodies led to the identification of a cDNA coding for a novel protein whose only homol. to known proteins is to the active site of trypsin-type serine proteases. The authors called this protein the novel serine protease (NSP). NSP exists in at least three differentially spliced forms, one of which is expressed predominantly in brain and testis. Immunohistochem. and immunopptn. with antibodies generated against NSP show that it is expressed and secreted by a variety of cells and that, in brain, it is found primarily in cerebrovascular smooth muscle cells and reactive astrocytes.

L21 ANSWER 25 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1998:46025 Document No. 128:152094 Peptidases in human bronchoalveolar lining fluid, macrophages, and epithelial cell: dipeptidyl (amino)peptidase IV, aminopeptidase N, and dipeptidyl (carboxy)peptidase (angiotensin-converting enzyme). Juillerat-Jeanneret, Lucienne; Aubert, John-David; Leuenberger, Philippe (Division of Pneumology, Department of

Internal Medicine, Centre Hospitalier Universitaire Vandois, Lausanne, Switz.). Journal of Laboratory and Clinical Medicine, 130(6), 603-614 (English) 1997. CODEN: JLCMAK. ISSN: 0022-2143. Publisher: Mosby-Year Book, Inc..

AB The modulation of proteolytic activity is an important factor in regulating the metab. and function of peptide-hormones. In this study, the activities of dipeptidyl (carboxy) peptidase (angiotensin-converting enzyme (ACE)), aminopeptidase N (APN), and dipeptidyl (amino)peptidase IV (DPP IV) were measured in the blood, the human bronchial epithelial and alveolar cells, bronchoalveolar macrophages, and the sol. phase of bronchoalveolar lavage (BAL) samples obtained from normal human volunteers and patients with pulmonary pathol. conditions. BAL fluid expressed ACE activity and very low levels of APN and DPP IV activities in the volunteer population, but higher levels could be measured in samples from patients. In patients, increased APN corresponded to a high granulocyte count, while DPP IV and ACE were assocd. with a high percentage of lymphocytes. Neither AIDS nor smoking induced on increased level of these enzymes. Immunohistochem. staining of bronchoalveolar smears with anti-human ACE monoclonal antibody showed that only macrophages expressed this enzyme. Enzyme histochem. for DPP IV and APN showed that all leukocytes expressed these activities. APN, DPP IV, and ACE activities were also found in cell exts. of bronchoalveolar macrophages. In exts. of bronchial epithelial and alveolar cells, only APN and DPP IV activities were detected. Kinetic properties of the sol. enzymes in lavage supernatants were comparable to those of serum enzymes. These results demonstrate that sol. forms of cellular enzymes found in BAL fluid are regulated independently in blood and that different cell types may release these enzymes.

L21 ANSWER 26 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN

1997:667899 Document No. 127:344627 Cathepsin B, thiols and cysteine protease inhibitors in squamous-cell lung cancer. Krepela, E.; Prochazka, J.; Karova, B.; Cermak, J.; Roubkova, H. (Department of Molecular and Cellular Pneumology, Clinic of Pneumology and Chest Surgery, Medical Faculty Hospital Bulovka, Prague, 180 71, Czech Rep.). Neoplasma, 44(4), 219-239 (English) 1997. CODEN: NEOLA4. ISSN: 0028-2685. Publisher: Slovak Academic Press.

AB The authors investigated activities of the cysteine protease cathepsin B (CB; EC 3.4.22.1), the levels of reduced glutathione (GSH) and cysteine and the activity of .gamma.-glutamyltransferase (.gamma.-GT; EC 2.3.2.2.) in squamous-cell lung carcinoma (SQCLC) and the lung parenchyma specimens from surgically treated patients. The basal CB activity, assayed in tissue exts. in the absence of exogenous activators, was significantly higher in SQCLC compared to the lung. The residual CB activity, remaining in tissue exts. after preincubation at 37.degree., was not any longer significantly different in SQCLC and the lungs. The inhibited CB activity, calcd. as the difference between the basal and residual CB activities, was significantly higher in SQCLC compared to the lung. In the case of the cysteine protease cathepsin C (CC; EC 3.4.14.1), neither the basal nor the residual nor the inhibited CC activities in SQCLC and the lung were significantly different. Compared to CC, the powerfulness of endogenous cysteine protease inhibitors to inhibit CB was much higher in both SQCLC and the lung. The cysteine protease inhibitors from SQCLC and the lung which effectively inhibited CB could be related to the inhibitors with an apparent Mr ranging from 10,000 to 30,000. Isoelec. focusing studies indicated significant differences in the progress of inhibition of the activity of CB isoforms in SQCLC and lung parenchyma exts. The levels of both GSH and Cys were significantly higher in SQCLC compared to the lung and the level of GSH was significantly higher in Stage III tumors compared to Stage I tumors. The activity of .gamma.-GT was not significantly different in SQCLC and the lung but it was significantly higher in Stage I tumors compared to Stage III tumors and showed a significant neg. correlation with GSH level in SQCLC. Dithiothreitol did not increase the basal activity of CB from SQCLC and the lung which indicates that reversibly oxidized forms of CB do not accumulate in the tumors and the lungs. The basal activity of CB from SQCLC and the lung was competitively inhibited by Cys. Moreover, increasing Cys concns. had a modulatory effect on the basal activity of CB from SQCLC and the lung which was featured by Cys-induced inhibition of CB activity and by subsequent Cys-effected recovery of CB activity from its previous inhibition by Cys.

L21 ANSWER 27 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1997:300004 Document No. 127:14839 Identification and cloning of human placental bikunin, a novel serine protease inhibitor containing two Kunitz domains. Marlor, Christopher W.; Delaria, Katherine A.; Davis, Gary; Muller, Daniel K.; Greve, Jeffrey M.; Tamburini, Paul P. (Isnt. Bone Joint Disease Cancer, Bayer Corp., West Haven, CT, 06516, USA). Journal of Biological Chemistry, 272(18), 12202-12208 (English) 1997. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB Interrogation of the public expressed sequence tag (EST) data base with the sequence of preproaprotinin identified ESTs encoding two potential new members of the Kunitz family of serine protease inhibitors. Through reiterative interrogation, an EST contig was obtained, the consensus sequence from which encoded both of the novel Kunitz domains in a single open reading frame. This consensus sequence was used to direct the isolation of a full-length cDNA clone from a placental library. The resulting cDNA sequence predicted a 252-residue protein contg. a putative NH2-terminal signal peptide followed sequentially by each of the two Kunitz domains within a 170-residue ectodomain, a putative transmembrane domain, and a 31-residue hydrophilic COOH terminus. The gene for this putative novel protein was mapped by use of a radiation hybrid panel to chromosome 19q13, and Northern anal. showed that the corresponding mRNA was expressed at high levels in human placenta and pancreas and at lower levels in brain, lung, and kidney. An endogenous sol. form of this protein, which was designated as placental bikunin, was highly purified from human placenta by sequential kallikrein-Sepharose affinity, gel filtration, and C18 reverse-phase chromatog. The natural protein exhibited the same NH2 terminus as predicted from the cloned cDNA and inhibited trypsin, plasma kallikrein, and plasmin with IC50 values in the nanomolar range.

L21 ANSWER 28 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1997:257917 Document No. 126:312630 Hydrolysis of big endothelin-1 by a serine protease in the membrane fraction of human lung. Hanson, Gunilla C.; Andersson, Karl-Erik; Gyllstedt, Erik; Hoegestaett, Edward D.; Lindberg, B. Fredrik (Department Clinical Pharmacology, Lund University Hospital, Lund, S-221 85, Swed.). Regulatory Peptides, 68(1), 63-69 (English) 1997. CODEN: REPPDY. ISSN: 0167-0115. Publisher: Elsevier.

AB The hydrolysis of human big endothelin1-38 (big ET-1) was investigated in the membrane fractions from three human lung specimens. The hydrolysis products were identified by HPLC or by amino acid anal., peptide sequencing and mass spectrometry, and the contractile effects of synthetic big ET-1, synthetic ET-1 and the major metabolite were tested on isolated rabbit pulmonary arteries. The dominating hydrolysis product was identified as big ET1-31, formed by a chymostatin-sensitive enzyme. Soybean trypsin inhibitor also suppressed big ET1-31 formation, while two other serine protease inhibitors, 3,4-dichloroisocoumarin and aprotinin, had no (or a limited) inhibitory effect. Through a partly phosphoramidon-sensitive enzymic activity, endothelin-1 (ET-1) was formed independently of big ET1-31. On isolated pulmonary arteries, big ET1-31 had a contractile effect similar to that of synthetic big ET-1, with pEC50% values of 7.3 and 7.1, resp. The pEC50% value of ET-1 was 9.2. These results indicate that human pulmonary membranes, besides hydrolyzing big ET-1 to ET-1, also express serine protease activity that is responsible for the formation of the biol. active product, big ET1-31.

L21 ANSWER 29 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1996:7241 Document No. 124:197006 Human ClpP protease: cDNA sequence, tissue-specific expression and chromosomal assignment of the gene. Bross, Peter; Andresen, Brage S.; Knudsen, Inga; Kruse, Torben A.; Gregersen, Niels (Center for Medical Molecular Biology, Aarhus University Hospital and Faculty of Health Sciences, Skejby Sygehus, Brendstrupgardsvej, 8200, Aarhus N, Den.). FEBS Letters, 377(2), 249-52 (English) 1995. CODEN: FEBLAL. ISSN: 0014-5793. Publisher: Elsevier.

AB We identified three overlapping human expressed sequence tags with significant homol. to the E. coli ClpP amino sequence by screening the EMBL nucleotide database. With this sequence information we applied 5' and 3'-rapid amplification of cDNA ends (RACE) to amplify and sequence human clpP cDNA in two overlapping fragments. The open reading frame encodes a 277 amino acid long precursor polypeptide. Two ClpP specific motifs surrounding the active site residues are present and extensive

homol. to ClpP's from other organisms was obsd. Northern blotting showed high relative expression levels of clpP mRNA in skeletal muscle, intermediate levels in heart, liver and pancreas, and low levels in brain, placenta, lung and kidney. By anal. of human/rodent cell hybrids the human clpP gene was assigned to chromosome 19.

L21 ANSWER 30 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1994:292810 Document No. 120:292810 Cloning and sequence analysis of cDNA for a human homolog of eubacterial ATP-dependent Lon proteases. Amerik, Alexander Yu.; Petukhova, Galina V.; Grigorenko, Vitaly G.; Lykov, Igor P.; Yarovoi, Serge V.; Lipkin, Valery M.; Gorbalenya, Alexander E. (Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Science, Moscow, 117871, Russia). FEBS Letters, 340(1-2), 25-8 (English) 1994. CODEN: FEBLAL. ISSN: 0014-5793.
AB Overlapping cDNA clones contg. mRNA for a putative Lon protease (LonHS) were isolated from cDNA libraries prepd. from human brain poly(A)+ RNA. The detd. nucleotide sequence contains a 2814-bp open reading frame with two potential initiation codons (positions 62-64 and 338-340). The 5'-terminal 337-nucleotide fragment of LonHS mRNA is highly enriched with G and C nucleotides and could direct synthesis of the LonHS N-terminal domain. More likely this region promotes initiation of protein synthesis from the second AUG codon in a cap-independent manner. The amino acid sequence initiated at the second AUG codon includes 845 residues, over 30% of which are identical to those of eubacterial Lon proteases. Residues of the 'A' and 'B' motifs of NTP-binding pattern and a plausible catalytic serine residue are conserved in LonHS. Northern blot anal. revealed LonHS mRNA in lung, duodenum, liver and heart, but not in thymus cells.

L21 ANSWER 31 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1993:662122 Document No. 119:262122 Protease inhibitors suppress in vitro growth of human small cell lung cancer. Clark, David A.; Day, Robert; Seidah, Nabil; Moody, Terry W.; Cuttitta, Frank; Davis, Thomas P. (Coll. Med., Univ. Arizona, Tucson, AZ, 85724, USA). Peptides (New York, NY, United States), 14(5), 1021-8 (English) 1993. CODEN: PPTDD5. ISSN: 0196-9781.
AB The effect of the protease inhibitors Bowman Birk inhibitor (BBI) and aprotinin on the in vitro clonal growth of two human small cell lung cancer (SCLC) cell lines was investigated. In addn., the effect of BBI on growth factor processing of proGRP by SCLC cells and on mRNA levels for prohormone convertase 1 and 2 (PC1 and PC2) in SCLC cells was examd. The protease inhibitors BBI and aprotinin significantly decreased growth in both SCLC cell lines studied. In NCI-H345 cells, BBI appears to inhibit the processing of proGRP to GRP, as indicated by Western blot anal. NCI-H345 cells, BBI appears to inhibit the processing of proGRP to GRP, as indicated by Western blot anal. NCI-H345 cells, when treated with BBI (100 .mu.g/mL), also showed highly significant decreases of mRNA for PC1 and PC2 of about 50%. These data suggest that proteases serve an important role in the growth regulation of SCLC and that inhibitors of these proteases may be potent suppression of SCLC growth at the level of the gene.

L21 ANSWER 32 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1993:646376 Document No. 119:246376 Interaction of secretory leukocyte protease inhibitor with proteinase-3. Rao, Narayanam V.; Marshall, Bruce C.; Gray, Beulah H.; Hoidal, John R. (Med. Cent., Univ. Utah, Salt Lake City, UT, 84132, USA). American Journal of Respiratory Cell and Molecular Biology, 8(6), 612-16 (English) 1993. CODEN: AJRBEL. ISSN: 1044-1549.
AB Secretory leukocyte protease inhibitor (SLPI) is a 12-kD nonglycosylated serine antiproteinase secreted by cells of mucosal surfaces. In human lung, SLPI is present in the respiratory epithelium. It is the major barrier to tissue destruction mediated by the polymorphonuclear leukocyte (PMN) serine proteinases, elastase and cathepsin G, within the upper respiratory tract. The authors have recently described a third PMN serine proteinase, proteinase-3, that like elastase causes lung matrix destruction and exptl. emphysema. The current studies examine interactions between SLPI and proteinase-3. The results show that: (1) SLPI and its reactive-site variants have no or minimal inhibitory activity against proteinase-3; (2) native SLPI does not complex with proteinase-3; (3) proteinase-3 selectively degrades both native and oxidized SLPI; and (4) the cleavage of SLPI by proteinase-3 occurs at the peptide bond COOH-terminal to Ala-16 in the NH2-terminal domain of SLPI.

L21 ANSWER 33 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1993:469184 Document No. 119:69184 Activators of coagulation in cultured human lung-tumor cells. Seitz, R.; Heidtmann, H. H.; Maasberg, M.; Immel, A.; Egbring, R.; Havemann, K. (Dep. Intern. Med., Philipps-Univ. Hosp., Marburg, D-3550, Germany). International Journal of Cancer, 53(3), 514-20 (English) 1993. CODEN: IJCNAW. ISSN: 0020-7136.

AB Tumor matrix generation and tumor cell growth are supported by coagulation processes within the tumor tissue. Activators of coagulation were searched for in suspensions of 9 permanent human squamous-cell lung-cancer (EPLC 32M1, U1752), large-cell lung-cancer (LCLC 97TM1, LCLC 103H, U1810), and small-cell lung-cancer (N-592, H-526, DMS79, 86M1) cell lines. Incubation with these cells shortened the recalcification time in normal plasma (also in the presence of antibodies against tissue factor) or coagulation-factor-VII-, VIII-, IX- or X-deficient plasmas. The activators of coagulation in the 2 most active cell lines (U1752 and LCLC 103H) were further characterized in purified systems: the cleavage of chromogenic substrates, and the generation of markers of pro-thrombin activation were assessed. Three activators of coagulation were found in intact or sonicated cell suspensions and culture supernatants: (i) a tissue factor (TF)-like activity; (ii) an activity activating factor X, which in contrast to "cancer pro-coagulant" was not inhibited by iodoacetamide; and (iii) an activity-activating pro-thrombin, which was inhibited by the serine protease inhibitor PMSF and appeared to require plasmatic co-factor(s). The heterogeneous expression of coagulation activators by lung-tumor cell lines might be of significance for tumor biol. and response to therapy.

L21 ANSWER 34 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1991:630105 Document No. 115:230105 Cytolytic human lung lymphocytes: characterization of intragranular protease content and response to interleukin-2. Breite, Warren M.; Dal Nogare, Anthony R.; Yarbrough, William C., Jr.; Weissler, Jonathan C. (Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235-9034, USA). American Journal of Respiratory Cell and Molecular Biology, 3(6), 535-41 (English) 1990. CODEN: AJRBEL. ISSN: 1044-1549.

AB Recent attention has focused on a family of proteases present in the granules of natural killer (NK) cells, interleukin-2 (IL-2)-activated NK cells (LAK cells), and cytotoxic T lymphocytes (CTL). In the current investigation, lymphocytes were obtained from human lung parenchyma and peripheral blood. Following activation with IL-2 both groups of lymphocytes exhibited comparable cytolytic activity against K562 targets. Lysosomal granules obtained from these cells contained 2 serine proteases with mol. wts. of 30 and 28 kD. These proteases were capable of hydrolyzing benzyloxycarbonyl-L-lysine thiobenzyl ester (BLT-ester), a substrate of cytolytic lymphocyte proteases. When compared to blood, unactivated lung lymphocytes contained higher levels of protease content. Although IL-2 produced a significant increase in blood lymphocyte protease content, no change in lung lymphocyte granule protease activity was obsd. Thus, cytolytic lung lymphocytes contain high levels of lysosomal granule protease but differ from blood lymphocytes in the ability to increase protease content following activation with IL-2. The high level of protease content in cytolytic lung lymphocytes suggests that these cells could produce local tissue injury during the release of lysosomal granules.

L21 ANSWER 35 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1991:599102 Document No. 115:199102 Degradation of airway neuropeptides by human lung tryptase. Tam, Elizabeth K.; Caughey, George H. (Cardiovasc. Res. Inst., Univ. California, San Francisco, CA, 94143-0130, USA). American Journal of Respiratory Cell and Molecular Biology, 3(1), 27-32 (English) 1990. CODEN: AJRBEL. ISSN: 1044-1549.

AB Several lines of evidence suggest a possible role for mast cell proteases in modulating the biol. effects of neuropeptides. To explore the potential of such interactions in human airway, the activity of ***human*** tryptase, the major secretory ***protease*** of ***human*** ***lung*** mast cells, against several neuropeptides with proposed regulatory functions in human airway, was examd. Using highly purified tryptase obtained from exts. of human lung, the sites and rates of hydrolysis of VIP; peptide histidine-methionine (PHM); calcitonin gene-related peptide (CGRP); and the tachykinins substance P (SP),

neurokinin A (NKA), and neurokinin B (NKB) were detd. Tryptase hydrolyzes VIP rapidly at several sites (Arg12, Arg14, Lys20, and Lys21) with an overall kcat/Km of 1.5 .times. 105M-1s-1 and hydrolyzes PHM primarily at a single site (Lys20) with a kcat/Km of 1.9 .times. 104M-1s-1. Tryptase also rapidly hydrolyzes CGRP at 2 sites (Arg18 and Lys24) with a kcat/Km of 2.7 .times. 105M-1s-1. The tachykinins are not hydrolyzed by tryptase. These observations raise the possibility that tryptase-mediated degrdn. of the bronchodilators VIP and PHM combined with exaggerated mast cell release of tryptase may contribute to the increase in bronchial responsiveness and the decrease in immunoreactive VIP in airway nerves assocd. with asthma. The favorable rates of hydrolysis of CGRP suggest that tryptase may also terminate the effects of CGRP on bronchial and vascular smooth muscle tone and permeability.

L21 ANSWER 36 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1991:446847 Document No. 115:46847 The ***protease*** -antiprotease balance within the ***human*** ***lung*** : implications for the pathogenesis of emphysema. Gadek, James E.; Pacht, Eric R. (Coll. Med., Ohio State Univ., Columbus, OH, USA). Lung, 168(Suppl.), 552-64 (English) 1990. CODEN: LUNGD9. ISSN: 0341-2040.
AB A review with 50 refs. Crit. elements of the mechanisms of emphysema remain to be clarified. However, taken together, the existing evidence supports the concept that alveolar matrix destruction ensues as the regulatory interplay between oxidant and protease expression is subverted. The final common pathway of matrix destruction links the inherited and acquired forms of emphysema through the ultimate expression of unimpeded neutrophil elastase.

L21 ANSWER 37 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1989:551279 Document No. 111:151279 Studies on thiol ***protease*** inhibitor isolated from ***human*** ***lung*** cancer cell line. Yoshioka, Shinkichiro (Sch. Med., Hiroshima Univ., Hiroshima, 734, Japan). Hiroshima Daigaku Igaku Zasshi, 37(1), 199-215 (Japanese) 1989. CODEN: HDIZAB. ISSN: 0018-2087.
AB Thiol protease inhibitors were isolated from culture media and cell exts. of 2 human lung cancer cell lines and characterized. From the culture media of a human squamous-cell lung carcinoma cell line, LK-2, high- (.apprx.90,000) and low-mol.-wt. (.apprx.10,000) inhibitors were purified. The low-mol.-wt. inhibitor, which was specific for thiol protease and stable below 60.degree. and at pH 6-10, was the predominant activity. In LK-2 cell ext., only low-mol.-wt. inhibitor was detected. Neither high- nor low-mol.-wt. inhibitors from the culture media and cell ext. of LK-2 reacted with anti-urinary thiol protease inhibitor rabbit IgG or anti-.alpha.2-thiol protease inhibitor IgG in a double immunodiffusion test. High- and low-mol.-wt. inhibitors were also purified from the culture media for a human lung adenocarcinoma cell line, Luci-10, whereas in the cell ext., only low-mol.-wt. inhibitor was found. Daily examn. of the inhibitor activity in the culture media of Luci-10 revealed that the cancer cells at the stationary phase released the inhibitor 2-3 times more than at the growth phase. The low-mol.-wt. inhibitor purified from the culture media of LK-2 as well as serum .alpha.2-thiol protease inhibitor, urinary thiol protease inhibitor, and a microbial protease inhibitor E64, suppressed the incorporation of 3H-thymidine in LK-2 cells. On the contrary, serine protease inhibitors and urinary and soybean trypsin inhibitors had no effect on the incorporation. Thiol proteases, papain, ficin, and cathepsin B, stimulated the incorporation in LK-2 cells.

L21 ANSWER 38 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1988:405089 Document No. 109:5089 Identification of human lung mast cell kininogenase as tryptase and relevance of tryptase kininogenase activity. Proud, David; Siekierski, Edward S.; Bailey, Graham S. (Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21239, USA). Biochemical Pharmacology, 37(8), 1473-80 (English) 1988. CODEN: BCPCA6. ISSN: 0006-2952.
AB The authors have described previously the IgE-mediated release of kininogenase activity from purified human lung mast cells. Here, using supernatant fractions from mast cells stimulated with anti-IgE in the presence of deuterium oxide, this kininogenase was purified to homogeneity by gel filtration and heparin-agarose chromatog. and it was demonstrated that it is identical to tryptase, the major neutral ***protease*** of ***human*** ***lung*** mast cells. Tryptase and kininogenase activities co-chromatographed through both purifn. steps with equiv.

yields. The final purified kininogenase was free of detectable chymotryptic and carboxypeptidase activities and was identified as tryptase on the basis of SDS-PAGE amino acid compn. and inhibition profile. Three such prepns. of tryptase were all capable of releasing kinin from each of 2 different prepns. of purified, single-chain, human low mol. wt. kininogen. Kinin generation was optimal at pH 5.5 and was enhanced by heparin, which has been reported to stabilize tryptase. SDS-PAGE anal. of kininogen hydrolysis by tryptase revealed the formation of a diffusely stained region in the mol. wt. range of 60,000-65,000, rather than a discrete heavy chain band. Under optimal conditions, (pH 5.5) the 3 tryptase prepns. released 10-12 .mu.g kinin/h/mg but released only 2 .mu.g kinin/h/mg at pH 7.2. HPLC anal. revealed that the kinin released was bradykinin. The unique pH optimum of this reaction of a serine protease, however, raises doubts as to the physiol. significance of this activity.

L21 ANSWER 39 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN

1988:71163 Document No. 108:71163 Structure, genomic organization, and tissue distribution of human secretory leukocyte-protease inhibitor (SLPI): a potent inhibitor of neutrophil elastase. Ohlsson, Kjell; Rosengren, Margareta; Stetler, Gary; Brewer, Michael; Hale, Karin K.; Thompson, Robert C. (Malmo Gen. Hosp., Univ. Lund, Malmo, S-21401, Swed.). Pulm. Emphysema Proteolysis, 1986, [Conf.], Meeting Date 1986, 307-22. Editor(s): Taylor, Joseph C.; Mittman, Charles. Academic: Orlando, Fla. (English) 1987. CODEN: 56CQAT.

AB An elastase inhibitor that immunocross-reacts with bronchial mucus inhibitor was isolated from human parotid secretions. The purified secretory leukocyte protease inhibitor (SLPI) gave a single band on SDS-PAGE and acid-urea gels and a single peak on reverse-phase HPLC. The sequence of purified SLPI was detd. by Edman degrdn. and consisted of 2 highly homologous domains. The complete sequence of the SLPI gene was detd. using cDNA probes. This sequence suggested that the primary translation product is 132 amino acids in length with a signal sequence of 25 amino acids. Intron-exon junctions were also defined; 4 exons were identified, including the 2 functional domains. The distribution of SLPI in humans was examd. using a specific antibody. A low concn. of SLPI was obsd. in normal plasma, whereas SLPI comprised .apprx.90% of the protease inhibitory activity of normal bronchial mucus. Complexes of SLPI with elastase were found in purulent bronchial mucus. SLPI prodn. was localized to serous cells of submucosal glands in tracheal and bronchial mucosa. SLPI was also found in epithelium of bronchioles, effusions from ear infections, nasal secretions, mixed saliva, cervical mucus, and uterine fluid.

L21 ANSWER 40 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN

1987:495077 Document No. 107:95077 Interaction of human low molecular weight kininogen with human mast cell tryptase. Schwartz, Lawrence B.; Maier, Manfred; Spragg, Jocelyn (Med. Coll. Virginia, Richmond, VA, 23298, USA). Advances in Experimental Medicine and Biology, 198A(Kinins 4, Pt. A), 105-11 (English) 1986. CODEN: AEMBAP. ISSN: 0065-2598.

AB The capacity of purified tryptase, the major neutral tryptic ***protease*** of ***human*** ***lung*** mast cells, to serve as a kininogenase was examd. with purified human low-mol.-wt. kininogen (LMWK) as the substrate. Incubation of 25 .mu.g of tryptase with LMWK for 2-30 min, with or without heparin, yielded no net time-dependent kinin release as detd. on the estrous rat uterus. The 0.4 .mu.g of kinin seen represented <10% of that released from excess LMWK by 5 .mu.g of human urinary kallikrein in 5 min. Incubation at pH 5.5 with or without heparin did not alter this result. LMWK did not appear by SDS-PAGE to be cleaved by tryptase either in the presence or absence of heparin. In contrast to its action on HMWK, tryptase did not extensively cleave LMWK or destroy its reactivity with kallikrein.

L21 ANSWER 41 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN

1987:435583 Document No. 107:35583 Tryptase and kinin generation: tryptase from human mast cells does not activate human urinary prokallikrein. Schwartz, Lawrence B. (Med. Coll. Virginia, Richmond, VA, 23298, USA). International Archives of Allergy and Applied Immunology, 83(3), 321-4 (English) 1987. CODEN: IAAAAM. ISSN: 0020-5915.

AB The effect of tryptase, a neutral ***protease*** released from ***human*** ***lung*** mast cell secretory granules, on the tissue

prokallikrein present in human urine was examd. Tryptase was shown previously to lack activity against plasma prokallikrein. Purified tryptase was incubated with a concd. prepn. of urinary prokallikrein. No increase in kallikrein-like enzymic activity or immunoreactive tissue kallikrein was detected. Activation of urinary prokallikrein with trypsin served as a pos. control. Furthermore, preincubation or urinary prokallikrein with tryptase did not diminish the subsequent activation of urinary prokallikrein by trypsin. Therefore, tryptase neither activates nor destroys human tissue or plasma prokallikreins.

L21 ANSWER 42 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1987:171676 Document No. 106:171676 Human pituitary tryptase: molecular forms, amino-terminal sequence, immunocytochemical localization, and specificity with prohormone and fluorogenic substrates. Cromlish, James A.; Seidah, Nabil G.; Marcinkiewicz, Mieczyslaw; Hamelin, Josee; Johnson, David A.; Chretien, Michel (Lab. Biochem., Clin. Res. Inst. Montreal, Montreal, QC, H2W 1R7, Can.). Journal of Biological Chemistry, 262(3), 1363-73 (English) 1987. CODEN: JBCHA3. ISSN: 0021-9258.
AB A ***human*** pituitary-derived serine ***protease*** , immunol. identical to ***human*** ***lung*** tryptase (I), was found immunohistochem. to be assocd. with mast cells present in pituitary connective tissue. Western blotting combined with SDS-PAGE indicated the presence of multiple forms: a major 36,300-dalton form and 3 minor forms with mol. wts. of 32,400, and 33,400, and 34,600. Two major forms with mol. wts. of 35,600 and 34,100 were detected by affinity labeling with 125I-D-Tyr-Glu-Phe-Lys-Arg-CH2Cl. Treatment of the pituitary I prepn. with N-glycosidase F indicated that some of the mol. wt. heterogeneity results from N-linked glycosylation. The multiple mol. wt. forms appeared to have the same N-terminal sequence: Ile-Val-Gly-Gly-Gln-Glu-Ala-Pro. Pituitary I had an apparent mol. wt. of 110,000 by gel filtration on Sephadex G-200 in the presence of 0.3M NaCl, indicating that I may be a tetramer of 32,400-36,300-dalton subunits. However, this quaternary structure was not stable to gradient PAGE. Human pituitary I was so reactive toward synthetic tripeptide coumarin-contg. substrates contg. a pair of basic amino acids at the site of cleavage, such as benzyloxycarbonyl-L-Ala-L-Lys-L-Arg-4-methylcoumarin-7-amide (kcat/Km = 2.38 .times. 108 M-1 s-1), that Briggs-Haldane kinetics may apply. The reversible inhibitor NaCl at a concn. of 1M decreased the kcat/Km for benzyloxycarbonyl-L-Ala-L-Lys-L-Arg-4-methylcoumarin-7-amide to 6.53 .times. 106 M-1 s-1, which reflected a 100-fold increase in apparent Km. Based on active site titrn. with fluorecein mono-p-glanidinobenzoate-HCl, NaCl had no effect on the no. of accessible active sites. Substrate specificity studies with prohormones indicated that pituitary I has a preference for cleaving C-terminal to arginine or lysine residues which are preceded by a proline residue 4 or 6 residues N-terminal to the site of cleavage.

L21 ANSWER 43 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1987:62286 Document No. 106:62286 Investigations into the biochemical mechanisms of pulmonary emphysema: effects of cigarette smoke on enzymes and antienzymes in the lung. Janoff, Aaron (Dep. Pathol., State Univ. New York, Stony Brook, NY, 11794-8691, USA). Respiration, 50(Suppl. 1), 13-25 (English) 1986. CODEN: RESPBD. ISSN: 0025-7931.
AB A review with 47 refs. on the mechanism(s) causing emphysema in cigarette smokers. Circumstantial evidence is beginning to provide a tenuous link between smoking and the protease [9001-92-7]-antiprotease imbalance hypothesis.

L21 ANSWER 44 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1986:205326 Document No. 104:205326 The IgE-dependent release of a Hageman factor cleaving factor from human lung. Meier, Henry Louis; Flowers, Brian; Silverberg, Michael; Kaplan, Allen P.; Newball, Harold H. (Basic Pharmacol. Branch, USAMRICD, Aberdeen, MD, 21010, USA). American Journal of Pathology, 123(1), 146-54 (English) 1986. CODEN: AJPAA4. ISSN: 0002-9440.
AB Passively sensitized ***human*** ***lung*** fragments release a ***protease*** by an IgE-dependent mechanism which can cleave human Hageman factor (Coagulation Factor XII). This enzyme, lung Hageman factor-cleaving factor, was partially purified by ion exchange chromatog. and gel filtration and was a serine protease with an apparent mol. wt. of 12,000-13,000. This protease appears to be unrelated to any known

activator of Hageman factor by mol. wt. and inhibition profile and was distinct from an IgE-dependent prekallikrein activator, as well as the kininogenase activity defined as basophil kallikrein of anaphylaxis. Although it appears marginally capable of activating Hageman factor, it rapidly cleaves and inactivates the activated form so that the net effect is a loss of activatable Hageman factor. Apparently, diminished levels of Hageman factor that may be seen assocd. with IgE-dependent reactions can be due to digestion and depletion rather than activation, and other criteria for activation of the contact system must be employed.

L21 ANSWER 45 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1985:518717 Document No. 103:118717 Studies on the protease inhibitors in lung cancer tissue. II. Purification of thiol ***protease*** inhibitor from ***human*** ***lung*** cancer tissue. Okumichi, Tsuneo (Sch. Med., Hiroshima Univ., Hiroshima, 734, Japan). Hiroshima Daigaku Igaku Zasshi, 33(1), 17-30 (Japanese) 1985. CODEN: HDIZAB. ISSN: 0018-2087.
AB Thiol protease-inhibitory activity was significantly higher in exts. from human lung cancer tissue than in that from normal lung tissue, irresp. of the type and stage of the lung cancer. The thiol protease-inhibitory activity was found in the cytosol fraction. The inhibitor was purified from adenocarcinoma and squamous cell carcinoma by papain-Sepharose affinity chromatog. and Sephadex G-100 gel filtration. The purified inhibitor showed single protein band with mol. wt. .apprx.13,000 on SDS-polyacrylamide gel electrophoresis. Mol. wts. of 2 types of thiol protease inhibitors purified from normal lung tissue by the same procedure were .apprx.65,000 and 26,000. Antigenicity and electrophoretic mobility of the thiol protease inhibitor from lung cancer tissue were almost the same as those of the inhibitor from normal lung tissue and human plasma, as detd. by double immunodiffusion and immunoelectrophoresis using rabbit anti-(urinary thiol protease inhibitor) IgG. Though the antigenicity of the lung cancer thiol protease inhibitor was similar to that of the urinary inhibitor, their electrophoretic mobilities were quite different. The lung cancer thiol protease inhibitor markedly inhibited ficin, papain, and human liver cathepsin B, and weakly inhibited bromelain and rat serum thiol esterase, but did not inhibit serine protease.

L21 ANSWER 46 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1985:3643 Document No. 102:3643 Analysis of protease inhibitors in bronchial and alveolar regions. Doi, Hiroyuki (Sch. Med., Univ. Tokushima, Tokushima, 770, Japan). Shikoku Igaku Zasshi, 40(4), 615-27 (Japanese) 1984. CODEN: SKIZAB. ISSN: 0037-3699.
AB Protease inhibitors were examd. in bronchoalveolar lavage fluid and bronchial lavage fluid from healthy portions of lungs of patients with localized lung diseases and in mucoid sputa from patients with chronic bronchitis. At least 2 protease inhibitors with mol. wt. of .apprx.13,000 and 50,000 were found in Sephadex G75 gel filtration of these fluids. The inhibitor with the lower mol. wt. was more stable against acid and heat than that with higher mol. wt., and was more potent in inhibiting neutrophil elastase than .alpha.1-antitrypsin (I). Elastase-inhibitory capacity of bronchoalveolar lavage fluid and mucoid sputum was mainly due to I and the low-mol.-wt. inhibitor, resp., whereas that of bronchial lavage fluid was shared by the 2 inhibitors almost equally. Ratios of the elastase-inhibitory capacity, low-mol.-wt. inhibitor, and I concn. to total protein was almost the same in bronchial lavage fluid and mucoid sputum, whereas those to albumin were significantly higher in mucoid sputum than in bronchial lavage fluid. The ratio of albumin to total protein in mucoid sputum was 1/5 of that in bronchial lavage fluid.

L21 ANSWER 47 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1984:586586 Document No. 101:186586 Alpha1-antitrypsin-protease interactions: the biological aspect. Arnaud, Philippe; Gianazza, Elisabetta (Clin. Immunol. Microbiol., Med. Univ. South Carolina, Charleston, SC, 29425, USA). Marker Proteins in Inflammation, 2, 181-201 (English) 1984. CODEN: MPINEG.
AB A review, with 82 refs., on the interactions between .alpha.1-antitrypsin and several serine proteases, including leukocyte elastase. The clin. consequences of .alpha.1-antitrypsin deficiency are discussed.

L21 ANSWER 48 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1984:566074 Document No. 101:166074 Human lung tryptase. Purification and

characterization. Smith, Timothy J.; Hougland, Margaret W.; Johnson, David A. (Quillen-Dishner Coll. Med., East Tennessee State Univ., Johnson City, TN, 37614, USA). Journal of Biological Chemistry, 259(17), 11046-51 (English) 1984. CODEN: JBCHA3. ISSN: 0021-9258.

AB Human lung tryptase, a mast cell-derived trypsin-like serine ***protease*** , was isolated from whole ***human*** ***lung*** tissue obtained at autopsy. Increased yields from this purifn. process allowed extensive characterization of the enzyme. One of the crit. steps in the purifn. scheme was the use of a linear heparin gradient to elute active material from cellulose phosphate. Gel filtration studies in 0.1M NaCl yielded an apparent mol. wt. of 135,000, and subsequent electrophoresis on SDS-polyacrylamide gels demonstrated the presence of 2 active species with apparent mol. wts. of 30,900 and 31,600. Enzymic activity was sensitive to NaCl concns. >0.05M and was only 50% in 0.15M NaCl, decreasing to 18% in 0.6M NaCl. The effects of synthetic and natural inhibitors were also studied, confirming the enzyme trypsinlike characteristics and demonstrating that naturally occurring serum inhibitors are incapable of diminishing its activity. A complete amino acid anal. showed a high tryptophan content. Lastly, antisera to human lung tryptase were generated, and the immunol. identity of active fractions was investigated as well as the localization of the enzyme to the mast cell granule by immunohistochem. staining.

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1984:470352 Document No. 101:70352 The injurious effect of neutrophils on pneumocytes in vitro. Ayars, Garrison H.; Altman, Leonard C.; Rosen, Henry; Doyle, Theresa (Dep. Med., Univ. Washington, Seattle, WA, 98195, USA). American Review of Respiratory Disease, 129(6), 964-73 (English) 1984. CODEN: ARDSBL. ISSN: 0003-0805.

AB To study the role of neutrophils in mediating pulmonary injury, these cells were cocultured with monolayers of human A549 pneumocytes and rat type II alveolar cells. As indexes of injury, cell detachment from monolayers, frank cytolysis, and the effect of pneumocyte protein and DNA synthesis were measured. Unstimulated neutrophils effected minimal lysis or detachment of both pneumocyte targets, but neutrophils stimulated with phorbal myristate acetate and other secretagogues produced marked target cell detachment without lysis, which was time- and dose-dependent. Supernatants of activated neutrophils were similarly effective, suggesting that the mediator was a stable, sol. substance. Catalase and superoxide dismutase were minimally inhibitory to neutrophil-mediated detachment, and neutrophils from patients with chronic granulomatous disease produced detachment comparable to that produced by normal neutrophils. Furthermore, target cells were quite resistant to reagent H2O2 and non-neutrophil-derived toxic O species, further suggesting that oxidative injury was not a major factor in causing detachment. Target cells were susceptible to detachment by the neutral proteases, elastase and collagenase, whereas neutrophil-mediated detachment was markedly inhibited by neutral protease and elastase inhibitors. Human and bovine serum were also inhibitory, but not albumin or pepstatin A, an acid protease inhibitor. Furthermore, activated neutrophils inhibited protein and DNA synthesis of pneumocyte targets, providing addnl. evidence that neutrophils cause nonlytic injury to pneumocytes. Thus, stimulated neutrophils cause nonlethal injury to pneumocytes, as measured by detachment from monolayers, and inhibition of vital intracellular synthetic functions. The mechanism of detachment is through the action of granule neutral proteases, rather than toxic O metabolites, and is probably due to degrdn. of the extracellular matrix of the pneumocytes. In vivo, detachment could lead to desquamation of alveolar cells and increased permeability of the epithelial barrier of the lung. Similarly, inhibition of protein and DNA synthesis could have profound effects on the normal function and replication of alveolar epithelium.

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1984:205565 Document No. 100:205565 Cleavage of the Arg1-Pro2 bond of bradykinin by a ***human*** ***lung*** ***peptidase*** : isolation, characterization, and inhibition by several .beta.-lactam antibiotics. Sidorowicz, Wladyslaw; Szechinski, Jacek; Canizaro, Peter C.; Behal, Francis J. (Sch. Med., Texas Tech Univ., Lubbock, TX, 79430, USA). Proceedings of the Society for Experimental Biology and Medicine, 175(4), 503-9 (English) 1984. CODEN: PSEBAA. ISSN: 0037-9727.

AB An aminopeptidase P (EC 3.4.11.9) that cleaves the Arg1-Pro2 bond of

bradykinin has been isolated for the 1st time from human lung and purified 473-fold. The enzyme also catalyzes the cleavage of arginine from des-9-arginine-bradykinin (I) and the hydrolysis of several X-proline dipeptides (X = unspecified amino acid), including L-Arg-L-Pro, L-Leu-L-Pro, and L-Ala-L-Pro. The purified enzyme was routinely assayed (after initial identification with I) with L-Leu-L-Pro. The mol. wt., in nondenaturing buffers, is 188,000 daltons. The pH optimum was 8.0 with Arg-Pro, and was 6.8 with Leu-Pro. Chelating agents do not inactivate the enzyme, but rather only remove loosely bound cations that stimulate the enzyme. Mn2+ is the principal cation that stimulates the enzyme. The enzyme is inhibited by several .beta.-lactam antibiotics, cephalexin and oxacillin being the most effective of those tested. The antibiotic inhibition is time and temp. dependent, and it is not fully reversible by exhaustive dialysis of the antibiotic-treated enzyme.

L21 ANSWER 51 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1983:502972 Document No. 99:102972 Proteases and antiproteases in the lung. Janoff, Aaron; Carp, Harvey (Dep. Pathol., State Univ. New York, Stony Brook, NY, USA). Lung Biology in Health and Disease, 19(Immunopharmacol. Lung), 173-208 (English) 1983. CODEN: LBHDD7. ISSN: 0362-3181.
AB A review with .apprx.155 refs. on the title topic. The effects of cigarette smoking on lung proteases/antiproteases are considered. The protease-pathogenesis model of chronic obstructive lung diseases also is discussed.

L21 ANSWER 52 OF 54 CAPLUS COPYRIGHT 2003 ACS on STN
1983:417889 Document No. 99:17889 Smokers do not have less functional alpha1-protease inhibitor in their lower respiratory tracts than nonsmokers. Stone, P. J.; Calore, J. D.; McGowan, S. E.; Bernardo, J.; Snider, G. L.; Franzblau, C. (Sch. Med., Boston Univ., Boston, MA, 02118, USA). Chest, 83(5, Suppl.), 65-6 (English) 1983. CODEN: CHETBF. ISSN: 0012-3692.
AB No differences were found between the mean values of .alpha.1-protease inhibitor (I) [9041-92-3] and total proteins of bronchoalveolar lavage (BAL) fluid of smokers and nonsmokers. However, unconcd. BAL fluid from smokers contained 140% as much porcine pancreatic elastase [9004-06-2]-specific I and 158% as much human neutrophil elastase-specific I as did BAL fluid from nonsmokers. Values of functional I, albumins, and proteins in concd. BAL fluid in smokers and nonsmokers were not different.

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1982:560519 Document No. 97:160519 Ceruloplasmin: plasma inhibitor of the oxidative inactivation of .alpha.-protease inhibitor. Taylor, Joseph C.; Oey, Lily (Respiratory Dis. Dep., City of Hope Med. Cent., Duarte, CA, 91010, USA). American Review of Respiratory Disease, 126(3), 476-82 (English) 1982. CODEN: ARDSBL. ISSN: 0003-0805.
AB When leukocyte lysosomal exts. are used as a source of elastase and are combined with a fraction of plasma contg. sufficient .alpha.1 protease inhibitor (.alpha.1-Pi) to inhibit all but 30-40% of the elastase amidase activity, elastolysis occurs at 69% of the rate of the uninhibited elastase controls (0.125 M NaCl; pH, 6.5). Proteolysis of elastin requires the presence of NaCl. At pH 8.6, elastolysis is decreased to 30-40% of free elastase controls by 1.0 M NaCl. At pH 6.5, on the other hand, elastolysis is increased to 83% of the control values by these higher NaCl concns. The activity of human leukocyte myeloperoxidase is optimal at pH 6 to 6.5 and at NaCl concns. between 0.25 and 1.0 M. Purified myeloperoxidase, .alpha.1-Pi, and elastase, in the presence of NaCl and H2O2, can reproduce this phenomenon at pH 6.5, suggesting that the occurrence of elastolysis in lysosomal ext.-plasma mixts. may in part be a result of the oxidative inactivation of .alpha.1-Pi by myeloperoxidase present in the lysosomal ext. Human ceruloplasmin, the major antioxidant of plasma, inhibits this myeloperoxidase-dependent reaction, without interfering either with free elastase activity or with the appearance of activity in plasma-lysosomal ext. mixts. at pH 8.6. The antioxidant activity of ceruloplasmin is inhibited by N3-. Antioxidants such as ceruloplasmin may be an important determinant of lung defense in persons chronically exposed to oxidants.

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1973:544619 Document No. 79:144619 Interrelations between the human alveolar macrophage and .alpha.-1-antitrypsin. Cohen, Allen B. (Med. Serv., San

Francisco Gen. Hosp., San Francisco, CA, USA). Journal of Clinical Investigation, 52(11), 2793-9 (English) 1973. CODEN: JCINAO. ISSN: 0021-9738.

AB Alveolar macrophages lavaged from ***human*** ***lungs*** contain ***protease*** activity at an optimum pH of 3.0 and possibly a lesser peak of activity at pH 5.5. Protease activity measured at pH 4.1 is inhibited by purified .alpha.-1-antitrypsin (I). Fluorescent antibody studies of human alveolar macrophages showed that I is present in normal alveolar macrophages. In addn., macrophages from a patient with a homozygous deficiency of I exhibited less fluorescence when incubated in autologous serum than the same macrophages incubated in normal serum. Macrophages from normal subjects showed maximal fluorescence when removed from the lung and addnl. incubation with serum did not increase fluorescence. These results implicate the human alveolar macrophage as a possible source of an enzyme that may cause emphysema in patients deficient in I. They also show that I has access to the alveolus in normal subjects.